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ORIGINAL ARTICLES.

STUDIES IN HUMAN CONSTITUTION.

V. The Psychological Panel.

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AND

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In previous studies from the Constitution Clinic[1] it has been shown that certain characters of bodily form, as determined by direct measurement and numerical indices differ widely between representatives of the gastric ulcer and gall bladder races. For example, individuals with gastric ulcer have a relatively narrow costal angle, a wide gonial angle, a narrow palate arch and long incisor teeth, while individuals with gall bladder disease display a relatively wide costal angle, a narrow gonial angle, a broad palate arch and short even incisors. Indeed, it may be said that in general the ulcer person is of a slender, gracile, asthenic habitus; the space between the eyes forms a satisfactory proportion with the width of the face and the chin then tapers from this widest area in a delicate pointing. The gall bladder person, on the other hand, tends in general more toward solidity of form. The ponderal index (weight, stature) is high, and a quality of flabby coarseness permeates the structure. The narrower space between the pupils presents a less pleasing proportional relationship to the width of the face. From the standpoint of morphology then it has been shown that gastric ulcer and gall bladder disease occur in two

entirely different physical types of man. It is well known that there is no absolutism in Nature, so that occasionally fusion of the types in various degrees may appear in certain individuals.

Having thus established the fact that there are notable differences in the anatomical panels of certain disease groups, it would be of great interest to find analogous differences in the psychological panels of these groups. The purpose of this preliminary study of the psychological panel of the gastric ulcer and gall bladder races is to present, first of all, a method, and, second, to show that distinct differences exist in the respective psychic patterns.

In approaching this phase of the subject of constitution, the great difficulty has been to devise a method which would enable the physician to catch and record the elusive quality of man's personality, or psychic pattern. Obviously this is not a function which can be measured by instruments of precision nor encompassed by a mathematical formula. Yet personality is a force so powerful and definite that all the world is poignantly aware of its distinguishing presence at every human contact. It is the most difficult quality of man to comprehend and in most descriptions its subtle essence is quickly lost.

There has been much valuable work done on the physical habitus of patients suffering from mental disease. Kretschmer[2] has recently focussed the attention of psychiatrists upon the bodily form and bearing of members of the two great divisions of mental disease. He showed in a fairly convincing manner that the schizophrenic (dementia præcox) people were, in general, slender and asthenic, whereas patients with affective (manic depressive) disorders were for the most part thick set. Numerous subsequent observers have been able to confirm Kretschmer's work more or less satisfactorily. Among the more extensive reports on this subject may be mentioned those of Raphael,[3] Shaw,[4] Wertheimer and Hesketh,[5] and Naccaratti.[6] The effort of these workers has been to correlate physical habitus with mental disease. In a way they may be said to have taken exaggerated or pathological personality patterns and attempted to fit them into the anatomic type.

Since there were no existing studies of quite similar nature upon which to model our investigations, it was thought best to adopt a method which could be easily modified from time to time as experience developed. The material for the work was drawn from the wards of a general hospital population of rather high-grade intelligence. It was striking to observe the spirit of eager coöperation which the patients displayed toward this sort of investigation. Possibly they felt a certain satisfaction in suddenly finding that they, themselves, as individuals, were persons of distinction rather than merely the producers of phenomena and excretions which provoked an objective and impersonal interest. Nevertheless, it is true, that through the agreeable haze of talking about themselves

they failed to sense the sharply drawn objectivity of the psychic examination. For various reasons it was impractical to use lengthy questionnaires or elaborate psychological tests. We, therefore, decided to employ a rather old method, which perhaps the psychologist, on the one hand, may criticize as being too observational and the psychoanalyst, on the other, will say is too superficial. It may well be that both these objections are valid, so that doubtless more precise and deeper studies should be made later on. The method, however, has the support of the essential experience of clinical medicine. It consists of a combination of the subjective ideas of the patient and the observations of the physician. We found that two or three interviews, each of at least an hour's duration, aided by information supplied by the ward nurse and social worker, have served to give a fairly comprehensive idea of the patient's personality. This study was facilitated greatly by the use of a systematic outline or guide,* but every effort was made to avoid that inflexibility which is the inherent weakness of any printed form. As a model, to begin with, Amsden's[7] "Outline for the Study of the Personality" was chosen. From time to time additions and changes have been made in the plan and scope of this outline, based in part on our new experiences and in part on suggestions from the writings of many psychiatrists and psychologists, especially those of Wells,[8] Jung[9] and Blanton.[10] Our thanks are due to Drs. T. W. Salmon and C. I. Lambert for many helpful criticisms and suggestions.

AN OUTLINE GUIDE FOR USE IN THE STUDY OF THE "PERSONALITY MAKE-UP" OF INDIVIDUALS WITH CERTAIN SOMATIC DISEASES.

By Robert B. McGraw, M.D.

The preliminary discussion varies.

Establish good feeling with patient and as much understanding of the problem as possible.

A story of the patient's life, including things of emotional, economic and social importance, early life and disease. It is important to find out how he differs from his own brothers and sisters (not faults, differences).

Intellectual Functions.

Learning: How far did he get in school? Why did he stop? (Gives idea as to traits as well as intelligence.) Did he learn easily? What subjects? Did he do well at mathematics, geography, literature, languages? How well did he do in positions? What sorts of positions?

* Compiled by R. B. McGraw.

Retention of things learned: Memory: How good? Has he tried to improve it? What type? Visual, auditory or experience? (Situations, names, faces, tunes, pictures?) Is there vivid mental imagery? Is his attention easily distracted? What by? (External things or internal things?) Does he concentrate well?

Application of things learned: Good common sense? Does he plan well or take things as they come? Spend money wisely? Is he hasty or deliberate in his judgment? Is his advice sought by others? Does he show foresight? Is he systematic? Is he dexterous or clumsy with his hands? Has he ever had an opportunity to handle men? Does he do it well?

Sense of reality: Attitude toward rights of others. Visionary? Matter-of-fact? Inventive? Dreamy? Fantasy? Night dreams? Vivid? Mystical elaborations. Sleep walking? Truthful, shrewd, dishonest, gullible? Is he introspective? Abstract, philosophic? Is his interest primarily in himself or in others? Are his decisions based on logical reasoning or on emotions?

Somatic Demands.

Pleasure, pain, likes and dislikes, sensuous gratification, libido—Minor demands: Eating, drinking, smoking, habits. Neurotic traits: Thumb sucking, nail biting, tics, aches and pains and how he bears them? Fussy about food? Desire for attention? Vanity? Desire for luxury or comfort? Is he squeamish for sights, odors, noises, tastes?

Demand for activity: Motor and psychomotor. Active? Impulsive? Talkative? Restless? Easily fatigued? Enthusiastic? Sluggish? Is he steady or does he work by fits and starts? Is he pugnacious or not? Rhythm, grace?

Sexual life: Modest, naive, prudish, lewd? Shy? Many love affairs, etc.? Masturbation? How managed? Why stopped? Affectionate or cold? Does he place any restraint on himself in regard to sex? Has he definite heterosexual urge? Is he effeminate? (Mannish if a woman?) Homosexuality?

Personal Attachments: (May or may not be considered a part of his sex life. Some people would consider it under Social Adaptation.) What are his friends like? Are they older or younger, more intelligent or less so? Was he attached to his father or mother? Why? Was he antagonistic to his father or mother? Why? Was he attached to his brothers or sisters? Why? Was he antagonistic to his brothers or sisters? Why? Was he attached to his whole family unduly? (Homesick?) Married life happy? If not, why not? What were the reasons if he did not marry?

Selfestimate.

Feeling of insecurity: Conscious feeling of insecurity: Is he timid or bashful? Does he feel ill-at-ease in a crowd? Does he feel that lack of brains or education, or physical disease, or deform-

ity, or lack of poise, or charm has hindered him in life? Is he easily flattered or otherwise suggestible? Dependent, trusting, hesitating, evasive, shy? Is he frank, conceited, proud, boastful, generous, friendly, quarrelsome, loyal? Has he many friends? Does he like to be alone or with others? Is he narcissistic? (Very vain, a prolonged masturbator, does he play for effect?) Is he selfish or generous? To what extent is he bound by principle? Is he unduly loyal to people, or institutions? Is he sensitive or touchy—easily teased? Irritable? Easily angered?

Subconscious feeling of insecurity: Is he reticent? Easily offended? Overprecise? Selfish? Penurious? Is he tactful or stubborn? Overcritical or suspicious? Does he think people treat him well?

Mood and Emotional Reaction.

Is he cheerful and optimistic or morose and pessimistic, as a rule? Is his mood stable or variable? Is he quickly excited (made glad or unhappy?) Has he a quick reaction time in response to stimuli, usually? Does he react positively to pleasurable stimuli? Does he react by anger, fear or indifference to painful stimuli or to unpleasant personal situations? Is he easily frightened? What is the effect physically when frightened; sweat, cold, nausea, lump in throat, hair stand on end? Are his moods quickly over or does he worry, brood or harbor grudges?

Adaptation Imperative.

How much ambition? Material or spiritual? Conflict? How much courage? (Moral and physical?) Persistence? How much initiative, resourcefulness, versatility? A leader or a follower? What would have been his chosen occupation? In what does he get his deepest satisfaction?

Recreations: What sorts desired? Active sports? Less active sports? Hunting and fishing? Intellectual games? Gambling? Reading? What sort of literature? Music? Theatre-going and acting? Humor? Of what sort, boisterous, whimsical? Art? Hobbies? Group activities? Competitive activities?

Balancing factors: Religious observances? Political activities? Philosophic interests? Moral or social uplift work?

Conscious restraint of instincts: Does he control with great effort his appetites (food, drink, sexual), his fear or his anger, or does he allow these full play?

Special Traits.

Drawing, sculpture, architecture, music, poetry, dancing.

So far about 80 cases have been studied by this method, and of these 21 cases from the gastric ulcer group, representing 15 males and 6 females, and 12 cases from the gall bladder group, representing

5 males and 7 females, are here reported. Space does not permit the publishing of each personality study completely, but two examples are given to illustrate the method.

Case Reports. CASE I.—Male, aged twenty-nine years, a trucker, had a peptic ulcer as proven by operation.

Family History. Mixed stock: Father, English; mother, Irish.

Personal History. Brought up in New York City. Started to smoke at eleven years of age. Masturbated from fourteen to seventeen, when he had his first sex experience. Mother died when patient was eighteen. At nineteen, patient had a quarrel with his father, because the latter married again, and he left home. Married at twenty-three years of age. Soon after patient was discharged from the army. He has one daughter who was born after four years of married life. She has webbed fingers, a thing that the patient says has preyed on his mind. She has had convulsions too.

He now directs traffic at the American Railway Express Company's station, but formerly he was a guard on an armored truck and for two years "he sat on a safe and carried a gun." He was once followed by a car with four men in it.

Make-up. Was never a leader in school, but did average work. His memory is average. Judgment is hasty. Is extravagant and never saves any money. Has difficulty in executive work because he gets excited and feels that others will not take him seriously. He is somewhat inclined to exaggerate.

He is very irregular in his food habits, overeats and drinks a great deal of coffee. He says that he was always a great meat eater. He is usually active and energetic. His demand for sex gratification is rather great. He feels somewhat at a disadvantage in respect to his education. He is rather prejudiced in his views, and is probably rather negatively suggestible. He seizes opportunities rather well. He is usually optimistic, but has rather marked swings. He is very quick-tempered and rather easy to frighten, and quite soft-hearted. His ambitions are not very high. He has good recreative facilities. He controls his instincts very poorly.

Summary. Concentration rather good, hasty in judgment, extravagant. Overindulges his appetites, is overactive, highly sexed heterosexual. He is probably an opportunist. He is optimistic, changeable in mood, very quick tempered. Rather easy to frighten and very soft-hearted. He has little ability to control appetites, fear or anger.

CASE II.—Male, aged thirty-four years, a Y. M. C. A. secretary, had gall bladder disease, as proven by operation.

Personal History. He was the youngest of a family of fourteen and youngest of eight children born of his own mother who was his father's second wife. Born on lower East side, New York, in a tenement and in an environment of extreme poverty. At the age of seven years, he started school and also began to work as a newsboy. He says that he had no play periods, could not play baseball or swim and derived most of his enjoyment from his work—was very ambitious. Says that he frequently quarrelled and fought with his brother.

At fourteen years of age, he left grammar school, after graduation, and went to work as a clerk, going to evening high school. At about 1906, when the patient was sixteen years of age, his father was found unconscious, and later became psychotic, assaultive and was committed to a psychopathic hospital. He died after two years. He says that he first began to "have fun" at this time and to be really happy. Became interested in an orchestra and in choir singing. Sunday afternoons he sang in hospitals and

for the comfort of bedridden people in private homes. He was making progress at his work also, and at twenty-two years he married a woman who was also a choir singer.

His sexual development was apparently slow; apparently voice and hair changes did not take place until sixteen or eighteen years, and he says that before he met his wife he "hated all women."

Personality. Intellectual Activities. There was no evident difficulty in school, probably he went farther than most with his opportunities. He does well in positions. Learns easily. He did his poorest work in grammar. Memory good, better in visual than auditory fields. Attention and concentration average and not remarkable. Has excellent common sense, plans easily, spends money wisely. Is hasty in judgment by choice because he says that if he deliberates he becomes blocked. He is quite dexterous with his hands, though is inferior to his brother. Quite good in executive work. Is probably not very visionary. Concerns himself with everyday problems and is scrupulously careful of the feelings of others, very honest and matter-of-fact except as regards religious faith.

Somatic Demands. Has always overeaten. Frequently has abdominal discomfort just from gorging. He does not drink alcoholic beverages or smoke. He is possibly a little vain, rather enjoys telling of his successes and hardships. Is not squeamish and does not desire comfort and luxury overmuch. Is afraid of high places. Has been extremely active, energetic, ambitious, enthusiastic and steady in his activity. Not pugnacious now, but states he was so in his boyhood. Not fearful. He is not probably active naturally, must have a definite object; on vacations he *does* nothing. Says he hated women. Is modest and probably rather cold as regards heterosexual contacts. No love affair except that with his wife. Apparently needs no restraint on sex. Has a tenor voice and is definitely effeminate. Friends are older and better educated males. Much attached and devoted to his mother. Not attached to his sisters; rather close to his brother. Married life happy.

Self-estimate. Not timid or bashful. Likes a crowd. Does not feel hampered by lack of education or poise. Somewhat easily flattered. Not evasive or shy; not hesitating. Friendly, very loyal to people. Usually does not like to be alone. Very generous. Extremely rigid as to his principles. Not touchy or easily teased. Not penurious. Probably quite tactful. He says that as a child he had unbounded self-confidence, later he had more and that now he has a great deal, but that it is based on Christian faith entirely.

Mood and Emotional Reaction. Is uniformly cheerful and optimistic. Stable in mood,not quickly affected by emotions or moods. Reacts positively to pleasurable stimuli. He is made angry, by usual painful stimuli, but curbs his anger. He is not easily frightened by ordinary things and does not show physical symptoms of fear easily. He is apt to brood and worry overmuch and to repress things that disturb him.

Adaptation Imperative. Says he has always been very ambitious, as a boy it was for money and power, but now it is for spiritual attainment. He has considerable initiative and is generally a leader. Gets deepest satisfaction from his religion. Never enjoyed active sports, possibly because he never has an opportunity. Likes fishing. Never enjoyed gambling. Does not care to read. Loves music and the theater. Enjoys tinkering with his automobile very much. Very religious and devout. *Interested in social and moral uplift-work.* Never interested in politics. Has always been unable to control his appetite for food; fear and anger have not been problems.

Special Traits. Well-developed musical traits. Plays mandolin, violin and sings. No talent for graphic art.

CHART I.

	I. INTELLECTUAL ACTIVITIES.	
	Learning Ability.	
Dull	General learning ability	Exceptionally quick
	Memory.	
Poor	Experience memory	Exceptional
Poor	Visual memory	Exceptional
Poor	Auditory memory	Exceptional
	Concentration.	
Poor		Feverish
	Judgment.	
Poor foresight		Much foresight
	Planning Capacity	
Poor		Usually good
	Efficiency.	
Clumsy	Manual	Very dexterous
Poor	Executive	Exceptional
	Attitude Toward Rights of Others.	
Loose		Overscrupulous
	Attitude Toward Reality.	
Visionary		Overpractical
	Direction of Interest.	
All on self		All toward others
	II. SOMATIC DEMANDS.	
	Minor Appetites.	
Abstemious	Food and drink	Excessive
Naturally ascetic	Comfort	Loves luxury
Indifferent	Attention	Fervid
	Urge to Activity.	
Slow	Motor activity	Overactive
Lazy	Psychomotor activity	Overenthusiastic
	Character of Activity.	
Steady		Interrupted
Never fights	Aggressiveness	Pugnacious
	Attitude Toward Opposite Sex.	
Antagonistic	At ease	Bold
	Attitude Toward Same Sex.	
Attached to	At ease	Antagonistic
	III. SELFESTIMATE.	
	Selfconfidence.	
Timid		Overconfident
	Reaction to Wishes of Others.	
Suggestible		Ignores
	Gregariousness.	
Dependent on others		Solitary
	Subconscious Feeling of Insecurity.	
Touchy		Thick-skinned
	Frankness.	
Evasive, reticent, obsessions		Confidential, gushing
	Self-love.	
Narcissistic		Altruistic

Subordination to Sentiment.

Selfish	Generosity	Overgenerous
Cramped by principle	Principle	Opportunist

Loyalty.

Overloyal	Average	Disloyal

IV. Mood and Reaction to Pain and Pleasure.

Mood Type.

Pessimistic	Optimistic

Mood Stability.

Changeable	Unchanging

Excitability.

Quick	Slow

Reaction to Pleasurable Stimuli.

Becomes happy	Placid

Reaction to Usual Painful Stimuli.

Becomes fearful	Becomes angry

Emotional Stability.

Transient	Stable, worries, broods

V. Adaptation Imperative.

Desire for Selfassertion.

Ambitionless	Domineering
Passive-minded	Vigorous-minded

Recreative Activities.

Too few	Too many
Active Sports	
Less Active Sports	
Hunting or Fishing	
Intellectual Games	
Gambling	
Reading	
Music	
Theater-going or Acting	
Art	
Other Hobbies	

Balancing Factors.

Too few	Too many
(in addition to above)	or
Religious Beliefs	Inharmonious
Politics	
Philosophical Studies	
Moral or Social Uplift Work	

Conscious Restraint of Instincts

Repressive	Too little
Conquers fear	No attempt to control
Holds temper	Violent-tempered

VI. Special Traits.

Graphic Art.

No talent	Great talent
Drawing	
Sculpture	
Architecture	

Rhythmic Art.

No talent	Great talent
Music	
Poetry	
Dancing	

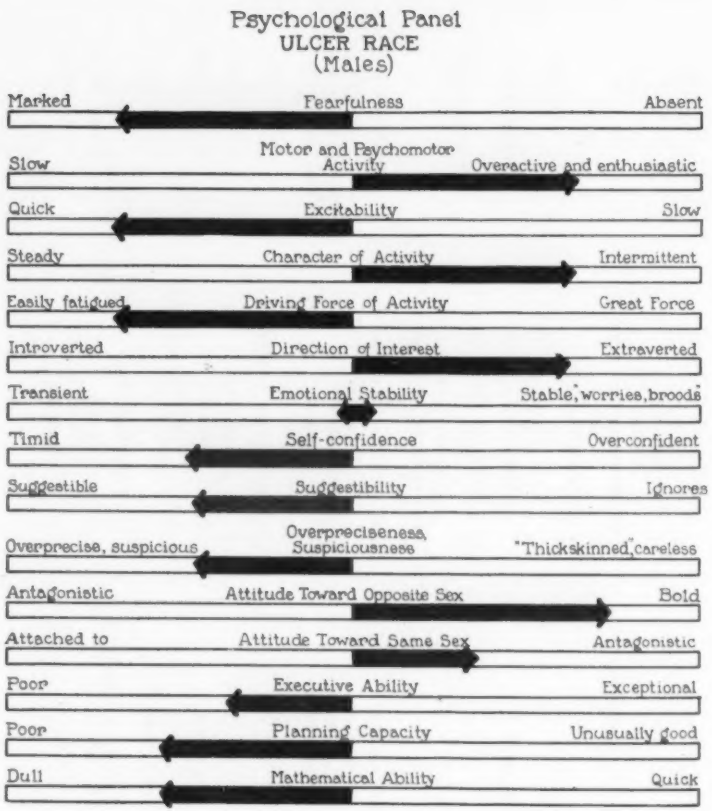


CHART II

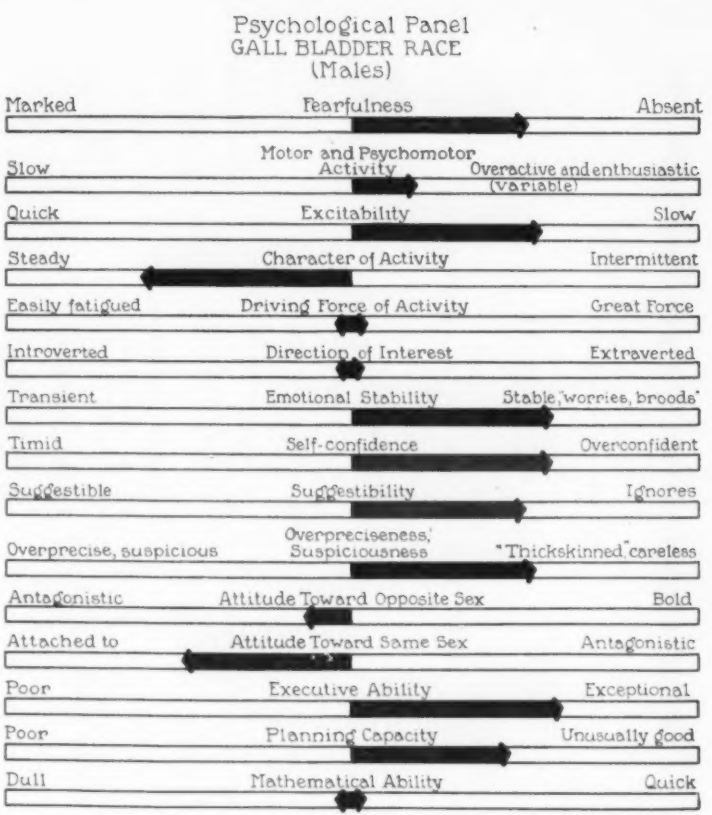


CHART IV

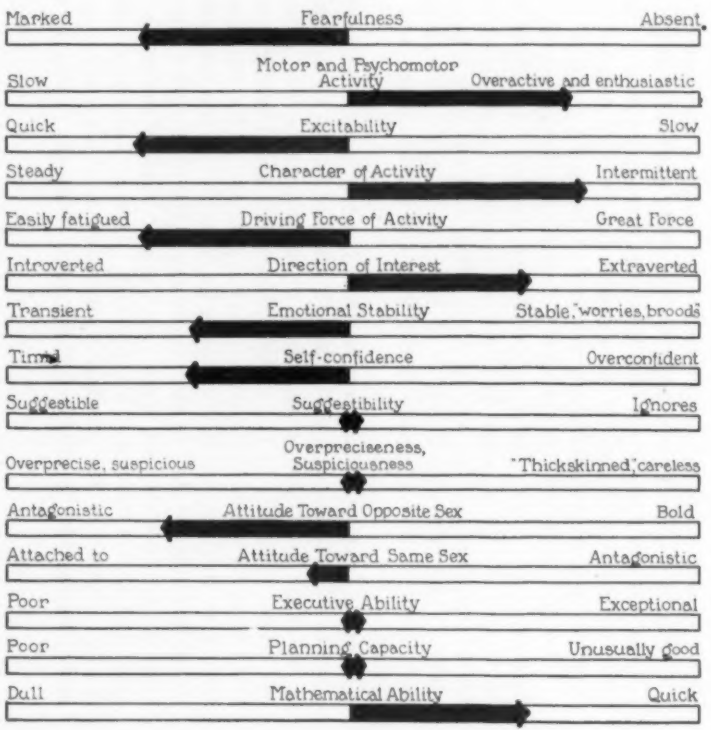


CHART III

CHART V

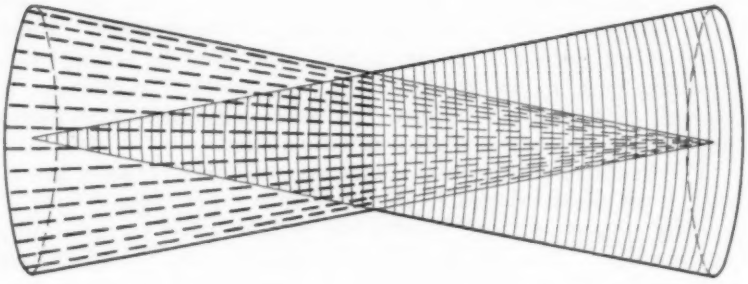
While much valuable information can be derived from the data in this form, it seemed desirable to express the characters in some graphic manner, which would indicate the direction and intensity of the traits. For this purpose the chart form devised by Smiley Blanton for the Child Guidance Clinic cases was used (Chart I). It is, of course, in the nature of things, not possible to measure or record personality in quantitative fashion. Yet qualitative estimation may often be so finely drawn that it matches in value the sharpness of mathematical proof.

Charts II, III, IV and V display the direction and suggested intensity trends of those qualities which have shown the greatest divergencies between the two disease races under discussion. It has been quite apparent throughout all the studies that variations are much less marked in the intellectual field than in other aspects of the total personality. The greatest differences lie in the zone of affective reactions or mood. Some of the most interesting and unexpected disclosures have been in the field of sex psychology, and these may be of considerable importance.

In order fully to understand the significance of these latter findings it is necessary to refer briefly to the condition of gynandromorphism. In a previous communication[11] it has been pointed out that not only was gall bladder disease between three and five times more common in the female, but that the morphology of those males who developed it was more or less strongly marked with female stamp. The appearance of femaleness within the male, or maleness within the female, is not limited apparently to the anatomic structures. Indications of opposite sex characters may crop out in any one or more of the four panels of personality and in any degree. This conception is diagrammatically shown in Charts VI and VII.

It should be realized at this point that the phenomenon of gynandromorphism is not related apparently to the procreative function. Successful ovulation may continue in the most strongly virilized women, and active spermatogenesis occur in markedly feminized males. The opposing qualities of male and female to which we have referred are expressed entirely in the somatoplasm and the psyche.

Now if Charts II and IV are compared, many notable differences appear. The quality of fearfulness (frightened easily by anything) is one of the outstanding attributes of the ulcer race, and is found but little, if at all, in the stolid, phlegmatic gall bladder people. With scarcely an exception, the psychic patterns of the two groups appear to be diametrically opposite in nature. In the field of sex it will be observed that in male members of the ulcer race there is a very strong heterosexual urge. In the gall bladder males, on the other hand, this interest is less marked. In a measure to translate the significance of the graphic representation of this tendency in ulcer females into its practical effect upon behavior, it may be said



Plastic schematic representation
of the
combined shifting values
of
masculine and feminine traits
in total personalities

≡≡≡ - Male
||||||| - Female

CHART VI

Schematic cross section of total personalities
Showing various degrees and distributions of opposite sex component

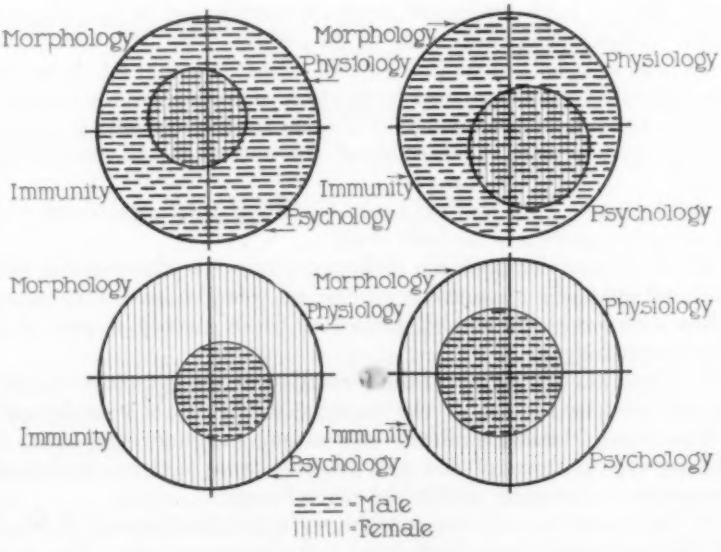


CHART VII

that several of our cases have been in individuals who have never been married or who have had poor marital adjustments. Among some of our male gall bladder patients the practical results of the feminine tendency are displayed in a certain lack of enthusiasm for strongly competitive activities. But such individuals often possess unusual sensitiveness and great artistic ability.

The qualities of executive ability and planning capacity are not well, if at all, developed in the ulcer race. For these people are quickly responsive, with intense but rapidly spent energies—ideal opportunists. The gall bladder representatives, on the other hand, plan well and are good executives, as one would expect in slow, methodical individuals. It is interesting in this connection to recognize that morphologically the gall bladder race corresponds closely with Kretchmer's pycnic type and the ulcer race with his asthenic or schizoid type. Rhumann[12] and also Tscherning,[13] in studying gastric ulcer, declare that their patients were asthenic and of Kretchmer's schizoid form and psychology. But we have seen nothing in the studies of the psychologic patterns of our cases which would suggest that the mental make-up of the ulcer race was schizoid or that the gall bladder people were necessarily syntonic.

In conclusion we wish to emphasize that definite differences exist in the psychic patterns of these two disease groups, gastric ulcer and gall bladder. Indeed, they are as definite as any differences which have appeared in the morphologic panel. Furthermore, it should be noted that combinations and overlappings of the qualities in the psychic patterns are found just as they were in the morphologic panel. Such gradations were frequently met in the morphologic studies. But they seem to be perhaps more frequent or at least less well-defined in the psyche. Notwithstanding, however, the difficulty of precise focus in the task of envisaging the imponderable elements of personality, it is none the less possible to gather and project a useful conception of the nature of the psychologic panel.

Conclusions. 1. A method is presented for studying and charting the psychic pattern of an individual.

2. There are demonstable differences between the psychic patterns of members respectively of the gall bladder and ulcer races. These differences are as well-defined as those already described in the morphology.

3. Elements entering into the formation of the gynandromorphic mosaic are found in the psychic panel as well as in the morphologic. There is considerable evidence of a strong feminine component in the psychic pattern of the gall bladder male and an analogous masculine component within the ulcer female.

4. In general, the psychic pattern of the gall bladder race displays stability of mood, little fearfulness and slow reactivity. The ulcer people, on the other hand, show less mood stability—rapid expendi-

ture of emotional energy—great fearfulness and quick adjustment to changes in their environment. They are ideal opportunists and mental sprinters; and, while they have little endurance, they are promptly rehabilitated by food, short periods of rest and the relief of anxiety.

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BONE DEVELOPMENT IN DIABETIC CHILDREN: A ROENTGEN STUDY.

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A ROENTGENOLOGIC study has been made of 68 diabetic children under fifteen years of age as a part of a study of diabetics of all ages. The original purpose was to look for the presence or absence of arteriosclerosis and to investigate the condition of the bones of adults. This led to a Roentgen examination of the legs, since sclerotic vessels are here so easily seen. So many diabetics showed abnormalities it seemed advisable to enlarge the scope of the research and to follow the course of diabetes from childhood to adult life. In addition, an attempt has been made to watch the development of the disease in the same individual from year to year. As we accumulated results our program was again expanded and roentgenograms have been made of the wrists and skull as well, so that

the material at present consists of Roentgen rays, for the most part, of the knees, tibiæ, fibulæ and tarsus, and in a few cases the wrists, hands and skull. An examination has been made of both legs, because occasionally an epiphysis appears in one before it appears in the other. We observed no other difference between the two legs except a rare anomaly.

Cohn's[1] standards for different age periods were selected. An advantage in using these standards is that one has roentgenograms with which to make comparison. One might expect that the epiphyses would appear later in northern children than in southern children, whom Cohn studied. That does not appear to be the case however, for, in examining the Roentgen rays of normal children, the epiphyses often appear earlier than in these standards, especially in the case of the os calcis. Cohn accepts Pryor's proof that there is a difference in time between epiphyseal development in the male and female—the female being considerably in advance of the male. It is generally accepted that epiphyseal age can be most accurately studied both in the living and after death by means of the Roentgen ray, although Stevenson[4] considers Roentgen ray shadows to be very confusing, and says that it is impossible to judge closure by this means. He also states that he found no difference in the time of union of the different races or sexes, and that "It is very probable that such differences if they exist are very slight."

The Roentgen age has been based on the time of appearance, size and conformation of the epiphyses and in older children upon the closure or partial closure of the epiphyses. Epiphyseal development and growth of shaft appear to go hand in hand.

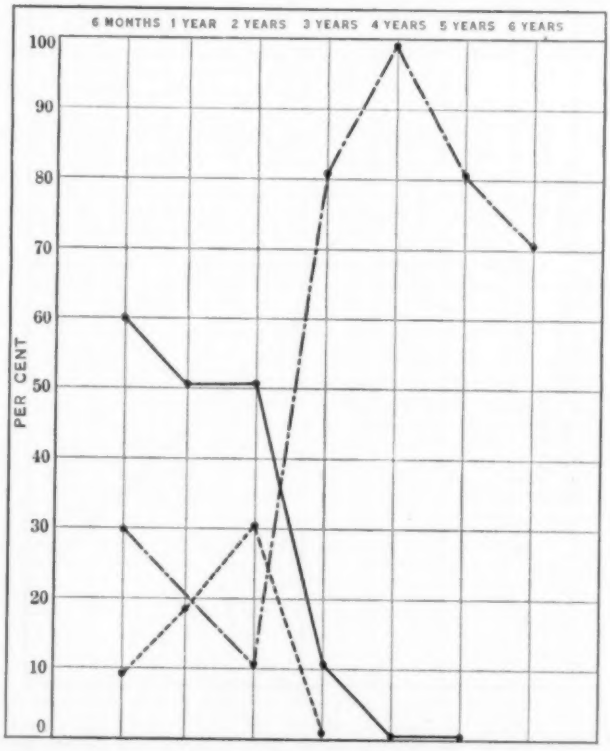
Delay of Development of Epiphysis and Shaft.—A delay of epiphyseal development and of shaft development in the cases of diabetes of long duration constitute our first observation. In direct contrast are the cases of recent onset in which the epiphyseal and shaft development appear to be in advance of the chronologic age. The latter findings are consistent with the measurements by Priscilla White,[5] made upon 100 diabetic children; 47 of our children were included in her group. She found that at the onset of the disease the diabetic child is taller than the normal child.

In order to show more clearly the effect which we believe to be the result of diabetes mellitus on epiphyseal development, that is, delayed epiphyseal formation, we present the chart on page 315.

It will be noted in Chart I that during the third year of diabetes there is a sharp rise in the percentage of cases under the chronologic age showing delayed epiphyseal development. Furthermore all the children who have not grown have had diabetes two years or more. In 8 of these the chronologic and Roentgen ages have corresponded. In the remaining 4 the Roentgen age is from one to three years below the chronologic age.

A variation of a year or more in the time of appearance of the epiphysis is considered within normal limits. The diabetic children are here, however, placed in separate groups, even when there is less than a year's difference in the time of the appearance of the epiphyses. This classification is made in order to show the trend

CHART I.



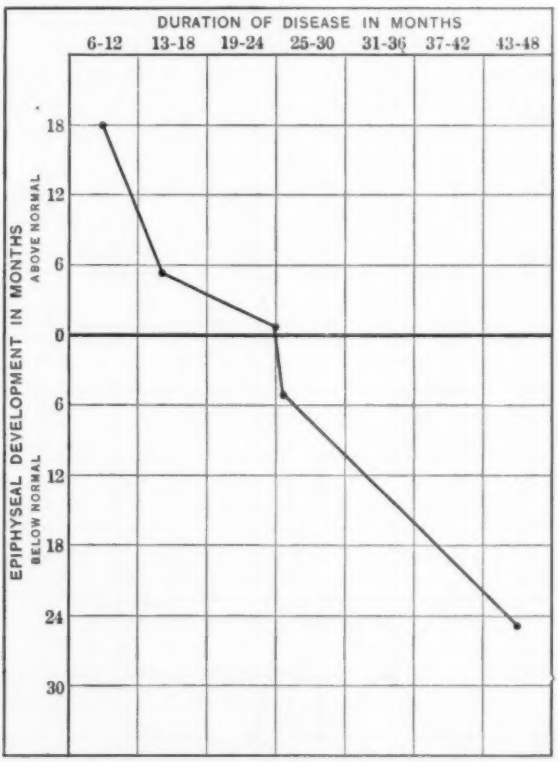
Percentages of cases: (1) ———— which were in advance of the chronologic age; (2) — — — — which correspond with the chronologic age; (3) —.—.—.—. which were under the chronologic age at varying periods of duration of diabetes.

toward delay or rapidity of development and not because the slight delay or rapidity is abnormal. The children are, then, grouped as follows:

Relation of epiphyses to chronological age.	Number of cases.
A year or more in advance	12
Up to one year in advance	15
Roentgen ray and chronologic ages correspond	10
Epiphyses delayed up to a year	20
Epiphyses delayed a year or more	11

Delay in the epiphyseal development in the diabetic as the disease continues is shown in Chart II:

CHART II.—EPIPHYSEAL DEVELOPMENT COMPARED WITH THE AVERAGE DURATION OF DIABETES MELLITUS.



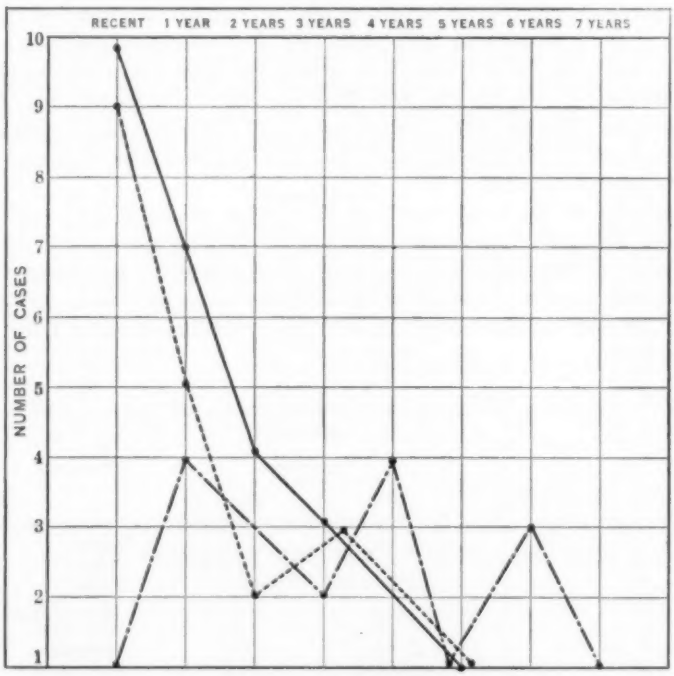
In Chart II it is shown that the epiphyseal development is eighteen months in advance of the normal in children with diabetes of six to twelve months' average duration. The epiphyseal development has dropped to normal in children with diabetes of two years' average duration. The epiphyseal development is retarded in children with diabetes, the average duration of which is over two years.

Nine of these 12 children, whose epiphyseal development is a year or more in advance of the normal, average 3.1 inches above standard height. One of the children is of standard height and 1 measures 1½ inches below standard. Eight of the 15 children, whose epiphyseal development is up to a year in advance of the normal, are 2.8 inches above standard. Four of these children are 1.7 inches under standard height. The heights of the 4 other children in these groups are not available.

Measurements of the diameter of the shaft and of the cortex anteriorly and posteriorly were made at the middle of the tibia. At this point the cortex proved consistently to be of the greatest width. Normally the diameter of the shaft and the thickness of the cortex increases yearly. We have determined the average measurement of the tibia for both boys and girls and by our findings have classified the children into three groups according to whether the measurements of the tibia are above, correspond with, or are below the standard.

These data we have also charted according to the duration of the disease.

CHART III.—SHAFT AND CORTICAL MEASUREMENTS OF DIABETIC CHILDREN ACCORDING TO THE DURATION OF THE DISEASE.



——·——·—— 25 cases whose measurements of the tibia are above the standard.
— — — — 20 cases whose measurements of the tibia correspond with the standard.
—.—.—.—. 19 cases whose measurements of the tibia are below the standard.

Chart III shows that only 1 child with diabetes of recent onset has measurements below standard, while 19 children are above standard. The percentage of cases above or corresponding to the standards decreases with each year of diabetes.

The diameter of the shaft is greater and the cortex heavier in

boys. The measurements of the shafts and cortices increase from year to year, except in cases of long duration. In children of the same age the cortical and shaft measurements vary according to the duration of the diabetes. That is, diabetics of recent onset have heavier shafts and thicker cortices than children of the same age who have had diabetes for two or three years.

The epiphyseal development does not correspond either to the width of the shaft or of the cortices. The measurements of the shafts and cortices do not correspond to the height of the child. This seems logical, since one sees such variety in the size and cortical thickness in persons of the same age and height.

Atrophy of the Bone. Atrophy of the bone was observed in 8 children. All of these children developed diabetes before eight and a half years of age and the duration of the disease in 6 of the 8 cases was three or more years standing and in 2 cases of a year or more. Two of these cases were mild diabetics, 2 were of moderate severity and 4 were severe in type. The incidence of infection was as great in another group of children who showed no atrophy and who developed diabetes before eight and a half years of age, so that it is believed that infection has no bearing on the production of atrophy in this series of cases.

Atrophy of the bone does not develop in children nine years of age or older, but why, we cannot say. There are several severe cases, even with long duration, in whom the disease developed after the ninth year and yet there is no bony atrophy. It is possible that atrophy of the bone is due to some condition other than the diabetes.

CHART IV.—ATROPHY OF THE BONE ACCORDING TO AGE OF CHILD AND DURATION OF DIABETES.

Age.		Duration.		Atrophy.
Yrs.	Mos.	Yrs.	Mos.	
5	..	3	1	+
5	..	1	..	Slight.
6	11	..	11	Slight.
8	11	5	10	Slight.
10	9	5	..	++++
11	6	3	5	Very slight.
11	1	4	6	Very slight.
11	1	4	2	Very slight.

Transverse Striæ. Transverse striæ were found in 36 of the 68 cases. The incidence of the striæ appears greater in these diabetic children than in the roentgenograms of children taken for fractures and other traumatic lesions. The slow growth of bone in the diabetic child may account for the high percentage of cases showing transverse striæ since these lines disappear more promptly in rapidly growing bones according to Martha Eliot[6] of the Yale Medical School.

Dr. Eliot has inspired us to search for a line occurring at the time of onset of the disease, but so far we have been unable to find such a line. The task is a difficult one, because so many of the patients had infections within a year of the onset of the disease. Since an infection would cause such a line, it is necessary to find cases in whom the onset was not immediately preceded by infection.

Conclusions. 1. Bone development is in advance of the chronologic age in children with diabetes of recent onset.

2. Bone development is below the chronologic age in children with diabetes of long standing.

3. Narrowness of the shaft and thinness of the cortex characterize the diabetic children of long standing.

4. Bone atrophy occurs in a certain number of children who develop diabetes before the ninth year, but has not been found above that age.

5. Transverse striæ of the bones are found in a larger percentage of diabetic children than of normal children, but we failed to associate a transverse line with the onset of the disease.

This study was made upon patients of Dr. E. P. Joslin.

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ERRONEOUS DIAGNOSIS OF RAYNAUD'S DISEASE IN OBLITERATIVE VASCULAR DISEASE (THROMBOANGIITIS OBLITERANS).

I. Vasomotor Disturbances Simulating Raynaud's Disease.*

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The difficulty of diagnosing localized vascular disease of the extremities may be attributed to failure to differentiate the vasomotor from the organic type, and failure to recognize the frequent

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association of these lesions in the same subject. The peripheral vascular disease may be divided into two main groups: (1) Obliterative or organic; (2) vasomotor or functional.

GROUP I. These cases may be divided into (*a*) thromboangiitis obliterans (Buerger's disease),[1] and (*b*) arteriosclerotic disease, (Table I). These have in common, symptoms due to insufficient

TABLE I.—TENTATIVE CLINICAL CLASSIFICATION OF ARTERIAL VASCULAR DISEASES.*

Functional or vasomotor types	Local distribution	Vasoconstricting types	1. Multiple-phase color reaction: Raynaud's disease. 2. One-phase color reaction: acrocyanosis, dead finger, local syncope.
		Vasodilating types	Erythromelalgia.
	General distribution	Vasoconstricting types	Primary or essential hypertension, early stages.
		Vasodilating types	Primary or essential hypotension.
Organic types	Local distribution		1. Arteriosclerosis, with or without thrombosis; diabetic gangrene. 2. Thromboangiitis obliterans (Buerger's disease). 3. Simple thrombosis or embolism. 4. Aneurysm with or without thrombosis.
	General distribution		Arteriosclerosis: 1. Primary. 2. Secondary to hypertension.

* In our experience this classification will cover practically all the usual forms of arterial vascular disease.

blood supply (excessive muscle fatigue or the pain of claudication) initiated by exercise. Pulsations in the main vessels are absent or diminished and rubor of the toes with dependency and blanching with elevation occurs. Minor trophic changes followed by dry gangrene usually occur. In cases of thromboangiitis obliterans immediately preceding or following trophic changes, the pain is usually continuous and excruciating, and often amputation is necessary for relief. In cases of arteriosclerosis in these stages the pain may be milder or entirely absent. Thromboangiitis obliterans is frequently associated with recurrent superficial phlebitis (35 per cent) and it is predominant in Hebrews (50 per cent). Arteriosclerosis is not associated with superficial phlebitis and is not predominant in any race. The patients are older, from fifty-five to eighty-five years of age, and the condition is associated with arteriosclerosis elsewhere. Patients suffering from Buerger's disease are younger, from seventeen to fifty years; and arteriosclerotic changes are rare.

GROUP II. The functional or vasomotor disturbances may also be divided into two groups, depending on the nature of the abnormal vasomotor reaction: (*a*) Vasoconstrictor; (*b*) vasodilator. In both groups the peripheral arteries pulsate normally, and color

changes are not initiated by change of position. The condition is recognized as Raynaud's disease when vasoconstriction is the primary disturbance and occurs symmetrically in the hands or feet with well-defined local color changes. Subjective symptoms and occasionally trophic changes are noted. Raynaud's disease is more common in females, and there are usually other evidences of vasoneurotic constitution. Milder vasospastic disturbances either primary, or secondary to obliterative processes in the arteries, are designated as "dead finger," "white finger," "acrocyanosis," or "acroasphyxia." In the vasodilator group the condition characterized by intermittent attacks of vasodilatation with redness and subjective symptoms of heat is known as erythromelalgia. There are probably two forms of the vasodilator disturbances, a primary or essential, and a secondary, associated with arteriosclerosis. The rubor in thromboangiitis obliterans is differentiated from that in erythromelalgia by the absence of heat, absence or diminution of pulsations in the palpable arteries, and the blanching with elevation.

Besides the two clinically defined groups of the organic or obliterative and the functional or vasomotor peripheral vascular disease there are two others in which vasomotor and obliterative vascular disease are associated, and in which obliterative vascular disease of the acral areas occurs without closure of the palpable arteries of the extremity. The latter group will be discussed in the following paper.

Basis and Purpose of this Study. Fourteen cases of thromboangiitis obliterans with well-defined vasomotor disturbance, constrictive in type, were studied. Nearly all the cases had been diagnosed Raynaud's disease elsewhere, even when closure of one or more of the main arteries of the extremities was evident. Edema or superficial phlebitis of the legs was present in 4 cases. In this group special studies were carried out. The histories of 3 cases are given in detail, and significant clinical data with regard to 11 are tabulated (Table II). The particular points emphasized in these studies are the frequent occurrence of vasomotor disturbances of a vasospastic nature in obliterative vascular disease, and further impairment of blood supply in extremities with occluded main vascular channels, due to actual vasoconstriction in the collateral channels.

Report of Cases. CASE I.—*Thromboangiitis obliterans of four extremities with a vasomotor disturbance of a spastic nature. Previous diagnosis: Raynaud's disease.* A man, aged thirty-eight years, came to the Mayo Clinic February 9, 1926, complaining of cold feet and hands. Three years previously, in the winter time, he had noticed numbness, coldness, and blanching and cyanosis of hands and feet on exposure to cold. Complete recovery followed the application of heat. There was no trouble in warm weather or when the body was kept warm. Eight months before admission he noticed arch fatigue and claudication after walking about 100 yards. Six months before admittance the ends of the fingers became definitely

TABLE II.—VASOMOTOR DISTURBANCES OCCURRING IN OBLITERATIVE VASCULAR DISEASE.

Case.	Age.	Pulsation in arteries.*										Vasomotor disturbances.
		Right.					Left.					
		Radial.	Ulnar.	Popliteal.	Dorsalis pedis.	Posterior tibial.	Radial.	Ulnar.	Popliteal.	Dorsalis pedis.	Posterior tibial.	
4	25	0	..	2	0	0	0	..	2	0	0	Index and fifth fingers on right hand became bluish and cyanotic when exposed to cold; color became normal when fingers were warm.
5	34	4	3	3	3	3	1	3	3	4	0	The great toe of the right foot showed marked pallor and moderate stinging pain when exposed to cold followed by return of normal color with warmth.
6	39	4	4	4	4	4	4	4	0	0	0	Great toe of left foot showed marked pallor when exposed to cold followed by blueness and gradual restoration to normal color with warmth.
7	35	4	2	2	1	0	4	1	0	2	0	Fifth fingers both hands became white and numb when exposed to cold followed by return to normal color with warmth.
8	38	4	4	3	2	0	4	4	2	0–1	0–1	Hands and feet became white and numb when exposed to cold followed by blueness and return to normal color with warmth.
9	51	4	4	0	0	2	4	4	0	0	0	Left foot and toes showed pallor when in warm bath followed by return to normal color at normal temperature.
10	51	4	4	4	4	4	4	4	0	0	0	Left foot and toes became white and painful when exposed to cold followed by cyanosis and normal color with the disappearance of pain with warmth.
11	28	4	0	0	0	0	4	4	0	0	0	Both feet showed pallor when exposed to cold followed by return to normal color with warmth.
12	57	0	0	2	4	4	0	0	Amputated			Both hands and feet showed marked pallor when exposed to cold followed by gradual restoration to normal with warmth.
13	33	3	0	1	0–2	1	3	0	2	0	1	Bluish discoloration of toes and fingers when exposed to cold followed by return to normal color with warmth.
14	40	4	4	4	4	4	4	4	4	1–4	1–4	Pallor of distal half and toes of left foot with exposure to cold followed by return of normal color with warmth.

* Graded from 4 to 0. 4 denotes normal pulsations and 0 denotes the absence of pulsations.

red when in the dependent position. At the same time a small ulcer appeared between the third and fourth toes of the left foot; it healed in six weeks and recurred. Superficial phlebitis, pain in calf or hand or so-called rest pain had not been noted.

On examination the hands and feet were cold and reddish purple; the skin was rough and thickened, and there was marked trophic change about the nails. There was a small superficial ulcer between the third and fourth toes of the left foot and two fissures in the skin of the left great toe. Pulsations in the arteries were graded from 4 to 0 (4, normal pulsations, and 0, absence of pulsations). Right radial, 0; right ulnar, 0; right popliteal, 4; right dorsalis pedis, 4; right posterior tibial, 2; left radial, 4; left ulnar, 2; left popliteal, 2; left dorsalis pedis, 2, and left posterior tibial, 2. The test for circulatory efficiency showed the right hand, when dependent, to be markedly bluish cyanotic and when elevated to be pale blue. The left hand when dependent showed Rubor III, when elevated Pallor III; the left foot when dependent showed Rubor III, when elevated Pallor III. The Wassermann reaction on the blood was negative. The urinalysis was negative and renal function normal; the blood was normal cytologically and chemically.

To test the color reaction of the hands, the patient was placed on a cold porch insufficiently clothed. As his body became chilled, his hands became extremely blanched with a subjective sensation of numbness and a "dead feeling." With an increase of environmental temperature the normal color returned in a few minutes accompanied by a sensation of tingling which gradually disappeared. The stage of cyanosis or incomplete recovery was not manifest.

Comment. This case demonstrates a true obliterative lesion of the arteries in which the disease was initiated with vasomotor phenomena of a vasoconstrictor type and in which the vasomotor disturbance persisted during the subsequent course of the disease. The vasomotor disturbances antedated the signs of arterial closure by two and a half years. The diagnosis of an obliterative lesion was based on the absence or diminution of pulsation in the main vessels, the color changes with dependency and elevation, and the symptoms of fatigue and claudication due to arterial insufficiency.

CASE II.—*Thromboangiitis obliterans affecting four extremities with associated vasomotor disturbance of the spastic type. Previous diagnosis: Raynaud's disease.* A locomotive engineer (Scotch), aged forty-six years, came to the Clinic February 17, 1926, because of an unhealed amputation wound of the third finger on the right hand and a small ulcer on the left thumb. Three winters previously he had noticed a feeling of numbness over the plantar surface of the left foot when he walked. Rest did not afford relief. Inspection showed the foot to be excessively pale. When warmed by air or water the foot returned to normal color with complete relief of the sensation of numbness. During the last winter a similar condition had developed in the right foot. The feet became red in the dependent position, and blanched when elevated. At no time had there been claudication, superficial phlebitis or rest pain. Six months before admittance he had sustained a traumatic injury to the third finger of the left hand, and it was amputated. Nine weeks before admittance an ulcer occurred spontaneously on the left thumb; this was severely painful for two weeks.

The feet were cold and the skin over the weight-bearing areas was thick

and rough. The toe nails showed marked trophic changes, and with feet in the dependent position the toes showed marked degrees of rubor. On elevation of the legs, marked pallor occurred. Some color was maintained in the left first toe. There were no pulsations in the left posterior tibial and dorsalis pedis arteries. The other vessels of the feet were apparently normal. The left radial and right ulnar arteries were obliterated. The left ulnar and right radial arteries pulsated normally. The hands were cold and there was marked trophic change involving the nails. There was an unhealed wound on the right fourth finger and an ulcer on the end of the left thumb. In the dependent position the fingers of both hands showed mild rubor; when elevated, marked pallor. The Wassermann reaction on the blood was negative. The urine and renal function were normal; the blood was normal cytologically and chemically.

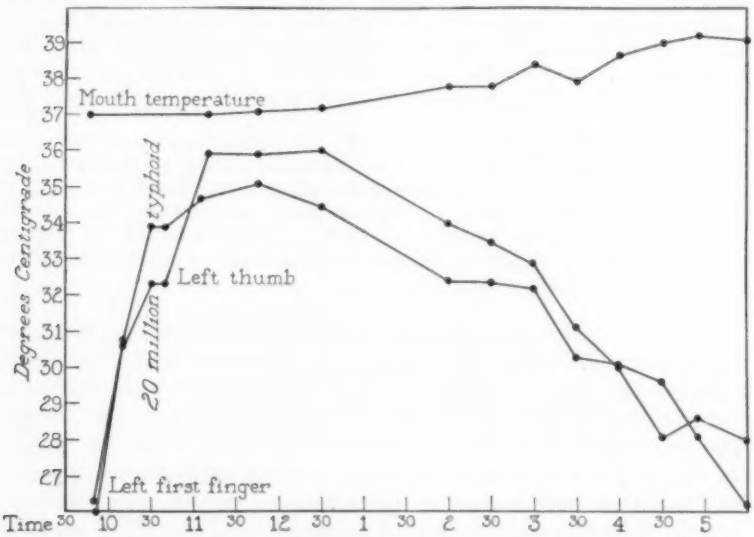

FIG. 1.—Mouth and skin temperature increase in thromboangiitis obliterans following the intravenous injection of foreign protein. The left radial artery was obliterated and the third finger was gangrenous.

After two weeks of medical treatment the patient was dismissed with instructions for the care of feet and hands. He returned in July 1926, complaining of increasing pain in the toes while at rest and progressive gangrene. Following the intravenous injection of foreign protein (typhoid vaccine) the temperature of the skin of the left thumb and first finger was markedly increased and pain was relieved (Fig. 1).

Lumbar sympathetic ganglionectomy and neurectomy was performed in July 1926. Improvement was marked. The pain disappeared and healing of the gangrenous areas initiated at once. The patient was dismissed with definite clinical evidence of increased bloodflow and relief of pain in the feet. The postoperative increase in the surface temperature of the feet was unchanged five months later.

Comment. This patient presented signs but no symptoms of an obstructive arterial lesion. The diagnosis was based on the constant absence of pulsations in the main peripheral arteries, the color changes with change of position, and gangrene. Signs of vasospastic

disturbance appeared, that is, pallor in the fingers followed by complete recovery. The obliterative disease was widely distributed, involving both the upper and lower extremities. The increase in the surface temperature of the fingers in excess of the increase of the blood temperature during the fever reaction indicated vasodilatation. This observation demonstrates that complete or maximal vasodilatation of the collateral vessels was not normally maintained or that excessive vasoconstriction existed. There was relaxation of these vessels as a response measure of the heat-regulating mechanism to fever. The favorable clinical response to an efficient vasodilating operation also bore out the assumption that lack of vasodilation or actual vasoconstriction as well as vascular occlusion contributed to the impaired blood supply.

CASE III.—*Thromboangiitis obliterans, with associated vasomotor disturbance of the spastic type. Previous diagnosis: Raynaud's disease.* A Dutch-English farmer, aged thirty-four years, came to the Mayo Clinic February 18, 1926, complaining of pain in the feet when he walked, and a painful ulcerated great toe on the right foot. Two years before admittance he had experienced a "tired feeling" in both feet brought on by walking and relieved by rest. This was accompanied by mild rest pain in the legs and feet, worse at night. One year prior to admittance he had noticed that the left foot became white and numb when exposed to the cold, and that after warming it became red and painful, then gradually became normal. The condition was always worse in cold weather. Six months before admittance an aching pain in the feet and calves with exercise occurred and gradually became more severe; it was relieved by rest. He was forced to do his work in "short stages" resting as frequently as possible. One month later his feet became swollen, and larger shoes were necessary. During the last four months the rest pain had been severe, and had interfered with sleep. For three months he had noted recurrent, superficial red spots on the legs, a hard "cord" beneath the skin, and tenderness to touch. At the same time a small ulcer appeared on the outer aspect of the right great toe; this had gradually enlarged and become gangrenous.

The patient's hands were cool and normally moist. The right and left ulnar, radial, and brachial arteries were pulsating normally. The feet were cold and red. The dorsum of the right great toe was gangrenous. The toes of the right foot showed marked rubor when dependent and pallor when elevated. The left foot showed moderate grade of rubor when dependent and pallor when elevated. In the right dorsalis pedis artery pulsations were small and intermittent. The right and left posterior tibial and left dorsalis pedis arteries revealed diminished pulsations.

Comment. Diagnosis was based on the existence of symptoms of vascular insufficiency (fatigue and claudication) diminished pulsations in the vessels of the feet, recurrent superficial phlebitis, early trophic changes and severe pain, and color change with change of position. None of these occur in functional vasospastic diseases of the extremities.

The vasomotor disturbance was of two types, pallor indicating closure of arterioles, capillaries, and venules, and a red stage representing dilatation of the surface capillaries and venules. Actual

dilatation of the arterioles was not demonstrated since increased surface heat did not occur in the red state. The intermediate or partial relaxation phase of cyanosis was lacking. The swelling in the feet indicated deep phlebitis with venous obstruction. There was also a definite history of superficial phlebitis which occurred in about 30 per cent of our cases of Buerger's disease. Thromboangiitis obliterans affects arteries, veins, and capillaries.

DISCUSSION OF TABULATED CASES (TABLE II).

CASE IV.—Examination of the nail fold capillaries in the stage of partial pallor (Fig. 2) disclosed a diminished number of visible capillaries for each unit area of skin. The loops were small and contracted, especially in the arterial limb. The flow was static and the erythrocytes were clumped, producing a segmental appearance of the capillary. In the stage of cyanosis (Fig. 3), the number of visible capillaries increased, the arterial limb showed slight dilatation while the venous limb was markedly dilated. The flow was resumed but slow, and was segmental in appearance. This probably indicates intermittent or incomplete relaxation of the precapillary arteriole. The microscopic examination of a cross-section of tissue of the amputated toe showed vascular occlusion by a thrombus, typical of thromboangiitis obliterans. There were many new-formed vessels (Fig. 4).

CASE VI.—The surface temperature studies with the thermocouple thermometer demonstrated marked increase in the skin temperature of both great toes following the intravenous injection of typhoid vaccine (Fig. 5). This is of interest in the presence of marked occlusion of the main arteries of the left foot, and indicates the existence of a vasoconstriction in the collateral vessels under usual conditions of environmental and body temperatures. Since there is an unsupplied demand for a greater blood supply with closure of the main arteries, it would be expected, *a priori*, that the collateral vessels would approach a maximum of vasodilatation at all times.

CASE VIII.—Microscopic examination of the arteries of the amputated extremity showed vascular occlusion by an organized thrombus with canalization. The walls of the artery and thrombus were infiltrated by lymphocytes and polymorphonuclear leukocytes (Fig. 6).

CASE XII.—Amputation of the third finger of the right hand was necessary. Microscopic examination showed evidence of old vascular occlusion with marked canalization and the formation of new vessels. Cellular infiltration was almost absent indicating that the reparative processes were almost complete (Fig. 7).

CASE XIII.—Amputation of the second and third toes of the right foot was necessary. Microscopic examination showed almost complete vascular occlusion and marked fibrosis (Fig. 8).

CASE XIV.—Amputation of the first and second toes of the left foot was necessary. Microscopic examination of the arteries of the toes showed almost complete vascular occlusion (Fig. 9).

Discussion. The association (30 per cent) of vasospastic disturbances with occlusive vascular disease is not widely recognized, although Buerger[2] called attention to this group and to the frequent errors in diagnosis. The failure to recognize the underlying organic lesion is inexcusable in the presence of nonpulsating vessels. When pulsations are present in the main vessels of the hands or feet,

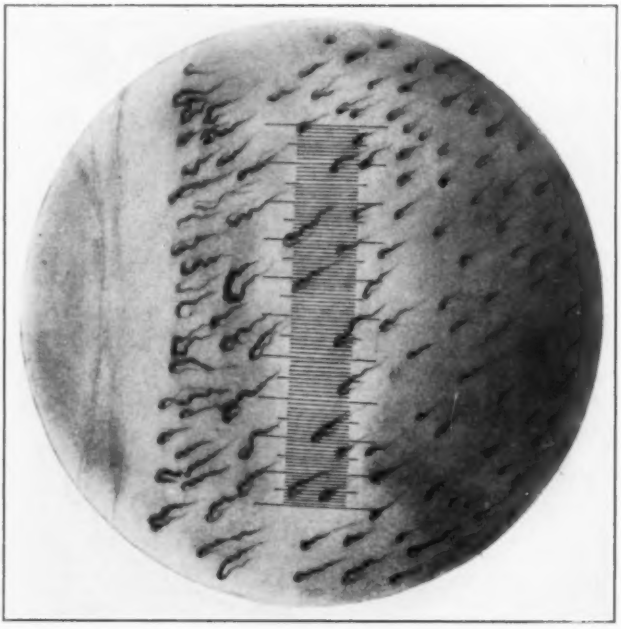

FIG. 2.—Nail fold capillaries in a case of thromboangiitis obliterans with vasomotor disturbances. Stage of pallor. Note the constricted loops, especially in the arterial limb, and the broken or segmented appearance of many loops. The flow was checked during the pallor stage.

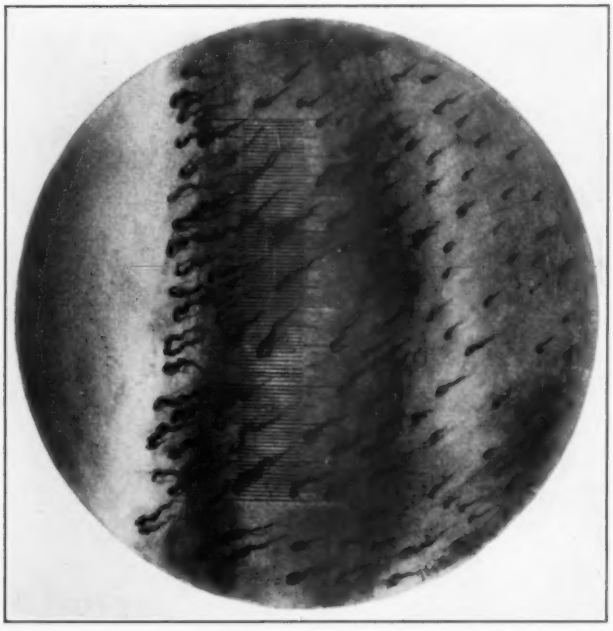

FIG. 3.—Nail fold capillaries in a case of thromboangiitis obliterans with vasomotor disturbances. Stage of cyanosis. Note the marked dilatation of the venous loops.

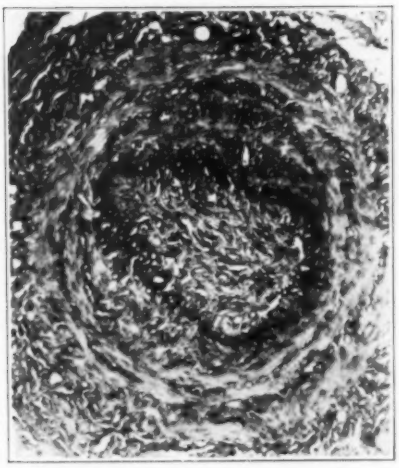

FIG. 4.—An artery from a toe of a case of thromboangiitis obliterans with vasomotor disturbances. Note complete vascular occlusion with many newly-formed vessels in the perivascular tissues.

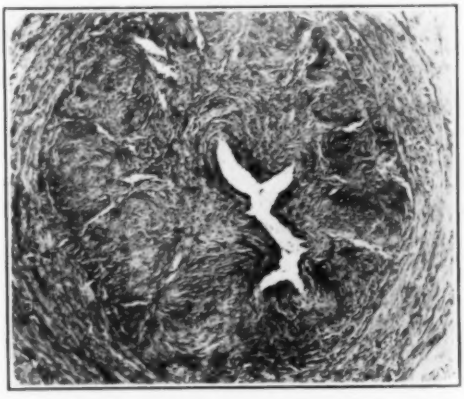

FIG. 6.—Vascular occlusion in a case of thromboangiitis obliterans with vasomotor disturbances. Partial canalization of thrombus.

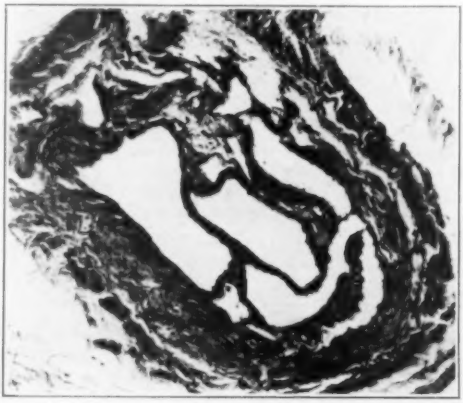

FIG. 7.—An artery from a finger in a case of thromboangiitis obliterans with vasomotor disturbances showing occlusion and marked canalization.

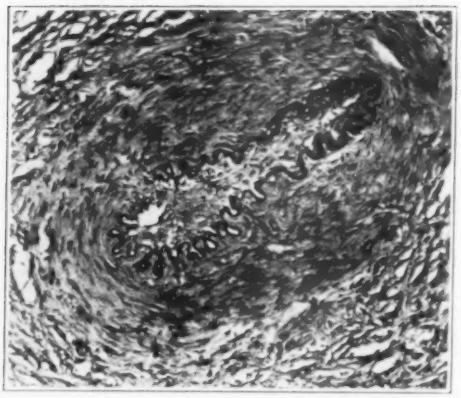

FIG. 8.—An artery from a toe of a case of thromboangiitis obliterans with vasomotor disturbances showing almost complete vascular occlusion and marked fibrosis.

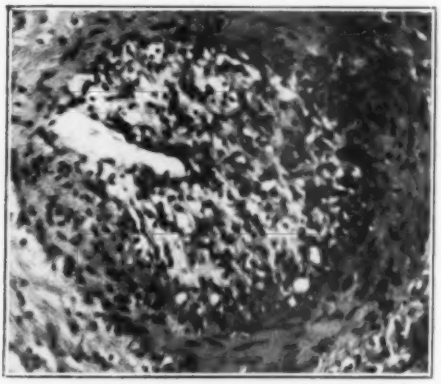

FIG. 9.—An artery from a toe in a case of Buerger's disease with vasomotor disturbances. The lumen is almost completely occluded by a fibrous mass firmly adherent to the vessel wall. Fibroblasts are numerous.

the diagnosis may be most difficult or only tentative. In such cases the diagnosis of an obliterative lesion (thromboangiitis obliterans) is indicated in the male subject if symptoms of vascular occlusion (excessive fatigue or claudication) of the digits, arch, or calf exist. Color changes with change of position, superficial phlebitis and trophic changes with continuous pain, are further confirmatory data of an obstructive vascular lesion, distal to the point of pulsa-

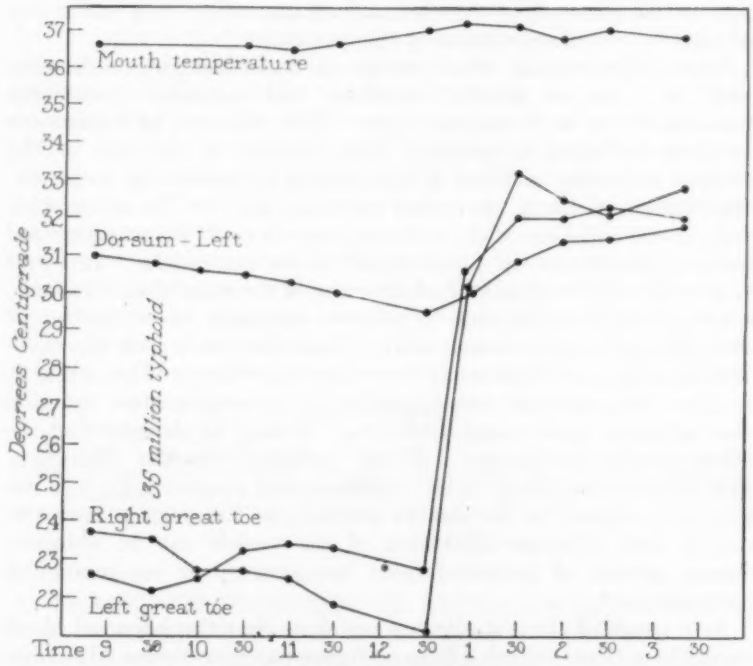
Mouth temperature
Dorsum - Left
35 million typhoid
Right great toe
Left great toe
Degrees Centigrade
Time 9 30 10 30 11 30 12 30 1 30 2 30 3 30

FIG. 5.—Marked increase in the skin temperature following foreign-protein injection in a case of thromboangiitis obliterans with vasomotor disturbances. The palpable arteries of the left foot were completely occluded.

tion. The signs and symptoms of arterial block are limited chiefly to the involved distal areas. There is never complete restoration of color. These signs and symptoms do not occur in primary vasomotor or functional disturbances, as Raynaud's disease, which is a functional disturbance. Except in the more advanced stages of Raynaud's disease restoration of bloodflow can be induced by the application of heat to the part. Cases reported as Raynaud's disease in which there is "spasm" of the palpable arteries of the hands or feet with absent or diminished pulsations for variable periods, are open to question in male patients.

Cases IV, VIII, XII, XIII and XIV with clinical evidence of a vasomotor disturbance of the spastic type showed conclusively microscopic evidence of arterial occlusion of the type characteristic

of thromboangiitis obliterans (Figs. 4, 6, 7, 8 and 9). These cases had been previously diagnosed Raynaud's disease. Case IV disclosed microscopic evidence of vasomotor disturbance of a spastic type (Figs. 2 and 3). The palpable vessels were pulseless, a condition never found in Raynaud's disease in our experience. The pathologic changes in the dissected vessels were characteristic of thromboangiitis obliterans (Fig. 4). In the remaining 9 cases there were clinical evidence of a vasomotor disturbance of the spastic type in the presence of pulseless vessels and other data indicating an organic or occlusive lesion of the vessels.

Acute inflammation which occurs in thromboangiitis obliterans could give rise to afferent impulses, and secondary vasomotor disturbances of a constrictor type. The existence of vasomotor reactions sufficient to produce color changes in the skin of the affected extremity indicate a high degree of vasomotor irritation. Observation of these vasomotor reactions lead to the assumption that vasoconstriction of the collateral vessels could be an additional factor in the diminished blood supply to the extremities. It would be assumed *a priori* that with obstruction of the main blood channels, a compensatory mechanism to produce maximal vasodilatation of the collateral vessels should occur. From our studies on the vasodilating responses obtained in fever there is evidence (Figs. 1 and 5) to show that maximal vasodilatation as a compensatory reaction does not exist under usual conditions. It may be thought that the rubor present in Buerger's disease indicates vascular dilatation. This is true with regard to the capillaries and venules only; it is not true with regard to the smaller arteries, as the surface temperature is low. Further dilatation of the vessels can be obtained during periods of increased body temperature or environmental temperature.*

As a result of these studies we conclude that the impaired blood supply in patients suffering from occlusive vascular disease (thromboangiitis obliterans) has a two-fold basis: that related to thrombosis in the main arterial pathways, and that due to the lack of maximal vasodilatation or in some instances, to actual vasoconstriction in the collateral channels. The foregoing data have led to further consideration of the efficacy of treatment, especially surgical, by interfering with the vasomotor paths. Lumbar sympathetic ganglionectomy carried out in selected cases of Buerger's disease induces increased blood supply to the feet. This would indicate an induced vasodilatation in the collateral channels.

Summary. Vasomotor disturbances, of a spastic type simulating Raynaud's disease frequently occur in extremities in which there is

* The exact basis of the compensatory rubor in obstructive vascular disease is not entirely clear. Buerger believes this is a compensatory dilatation of capillaries in an effort to increase the surface circulation. Our experiments corroborate those of Buerger in that capillary paralysis is not present as contraction of these vessels can be induced by various agents, mechanical and chemical.

conclusive evidence of organic vascular obliteration of the type characteristic of thromboangiitis obliterans. The association of vasomotor and organic disturbances leads to a high percentage of errors in diagnosis. The vasomotor disturbances may be an early sign of obliterative vascular disease. When a young male adult manifests vasomotor disturbances without evidence of arterial disease the diagnosis cannot be made, but thromboangiitis should be suspected. Cases in which vasospasm is associated with definite signs of vascular occlusion should present no particular problem in diagnosis if the frequency of vasomotor phenomena in thromboangiitis is recognized. The presence of diminished or absent pulsations in the palpable vessels indicates an organic or occlusive vascular lesion. The symptoms of vascular occlusion (excessive fatigue or the pain of claudication) phlebitis or color changes with change of position are confirmatory of the diagnosis of an obliterative lesion. These findings do not occur in the functional or vasomotor disturbances.

The recognition of vasoconstriction or the absence of maximal dilatation of the collateral channels in thromboangiitis obliterans is important. Our studies on the magnitude of the available vasodilatation in cases of thromboangiitis obliterans has been of service in the selection of cases suitable for lumbar sympathetic ganglionectomy.

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ERRONEOUS DIAGNOSES OF RAYNAUD'S DISEASE IN OBLITERATIVE VASCULAR DISEASE (THROMBOANGIITIS OBLITERANS).

II. THROMBOANGIITIS OBLITERANS OF THE LOWER EXTREMITIES WITH PULSATING PEDAL ARTERIES.*

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THE differential diagnosis of vascular diseases affecting the extremities is usually relatively simple. Primarily the diseases are divided into the organic or obliterative, and the vasomotor or

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functional. In about 90 per cent of the cases a clear division into the vasomotor and organic groups is made possible by the presence or absence of pulsations in the arteries that are usually palpable. In the remaining 10 per cent such division is difficult. In a previous paper[1] we presented a group of pathologically proved cases of thromboangiitis obliterans in which the main symptoms were vasomotor. The intermittent color changes of the hands or feet simulating those observed in Raynaud's disease were vasospastic in nature. The vasomotor symptoms were usually striking and often dominated the clinical picture. The true underlying organic disease of the main vessels had been entirely overlooked. In all the cases the diagnosis of Raynaud's disease had been made. The frequent occurrence of vasomotor disturbances in thromboangiitis obliterans (30 per cent) in the series led us to regard the diagnosis of Raynaud's disease in the adult male subject with considerable suspicion. The 8 cases presented here are largely of the type that make up the 10 per cent in which classification is difficult. This group includes the cases in which there are only slightly diminished or normal pulsations in the pedal arteries.

The first premise in the differentiation of the vascular disturbances of the extremities, as has been stated, rests on the presence or absence of pulsations in the arteries that are normally palpable. This premise is, however, subject to two qualifications: the disease must involve the arteries in or proximal[2] to the areas in which pulsations are felt normally, or pulsations may be present but greatly diminished or intermittent. The pathologic lesion in thromboangiitis obliterans often originates in the distal vessels of the feet. Gangrene may develop in the acral areas, when pulsations of the dorsalis pedis and posterior tibial arteries are apparently normal. Raynaud's disease is erroneously diagnosed in a high percentage of these cases. Buerger has cited cases of this type and has emphasized the difficulty of making a correct diagnosis.

Cases Studied. In the following 8 cases of thromboangiitis obliterans with pulsations in the main arteries of the feet the diagnosis was established by microscopic study. In 4 cases in which the arteries pulsated normally the histories and findings are presented. The significant points are tabulated, as are those of the remaining 4 cases, of which no histories are given (tabulation).

Case Reports. Case I.—*Thromboangiitis obliterans distal to the point of normal pulsations in the arteries of the foot: Amputation of toe with healing.* A man, aged forty-six years, came to the Mayo Clinic, September 6, 1925, complaining of pain, redness, and gangrene of the toes and feet. Three years previously he had suffered from a short attack of bilateral superficial phlebitis and following this his feet were cold and slightly blue. One year before admittance he had been awakened by severe pain in the left third toe, and on inspection found it bluish-black. This disappeared, but several times afterward the toe became deeply cyanotic and painful. It was not definitely gangrenous. Eight months later the second toe on the right

foot had been similarly affected; it healed but the symptoms recurred later. There had never been claudication or symptoms of fatigue with exercise.

At the time of examination both feet were cold, red, and swollen. The third toe on the left foot and the second toe on the right foot were gangrenous. Lymphangitis extended up the left leg in streaks and the nodes in the left groin were tender and red. The arteries of the legs and feet were pulsating normally (tabulation). Elevation of the feet caused Pallor II; in the dependent position there was quick return of Rubor III in the toes and distal half of the feet. The rate of heat elimination, determined by the foot calorimeter, was low. On microscopic examination of the nailfold capillaries an occasional dilated loop was found, but most of them appeared normal, with slight slowing of the rate of flow. The neurologic examination was negative. The Wassermann tests of the blood and spinal fluid were negative. The test of renal function showed 50 per cent return of the dye in two hours. The blood was normal chemically and cytologically except that there was slight leukocytosis during the course of the lymphangitis.

A diagnosis had been made elsewhere of diabetes, thromboangiitis obliterans, and nephritis. A tentative diagnosis was now made of thromboangiitis obliterans with sudden or acute thrombosis in the distal vessels of the toes. The lymphangitis was considered a sign of secondary infection. The lymphangitis, which extended to the left groin and was associated with febrile and leukocytic reaction, subsided under treatment. The following day there was another febrile reaction and an erysipelatous eruption appeared over the left knee. These symptoms disappeared in eleven days. The second toe of the left foot regained some normal color, but the third toe of the right foot remained gangrenous and was amputated. There was practically no bleeding when the incision was made and on microscopic examination practically all the small vessels of the toe showed occlusion by connective tissue containing many fibroblasts and a few leukocytes. There was slight canalization (Fig. 1) but marked vascularization in the surrounding tissue. Healing occurred by primary intention. The patient was dismissed from observation on the fifty-fifth day after admittance entirely free from pain and much improved in general health. One month later he stated in a letter that the third toe of the left foot was again semigangrenous; six months later he reported that a large ulcer had appeared on the left great toe, and he thought amputation would be necessary. Three months later the great toe of the right foot was amputated elsewhere.

Comment. Gangrene of the toes in the presence of normally pulsating pedal arteries is unusual and indicative of an obliterative lesion limited to the distal vessels of the feet and the toes. Absence of fatigue and intermittent pain in the arches or calves may mean absence of obliteration at a higher level. This history of a preceding superficial phlebitis makes the diagnosis of thromboangiitis obliterans tenable. The fairly sudden onset of pain and discoloration in the toes are symptoms of acute thrombosis. The degree of recovery depends on the establishment of collateral circulation which is manifested microscopically by the large number of small vessels in the wall of the occluded artery and the perivascular tissue (Fig. 1). Simple embolism could not be excluded, but the absence of a demonstrable primary focus, the recurrence in the same situation and in the opposite foot and the progressive nature of the process ruled it out. Amputation of the toe was justified in the presence of open vessels proximally.

THROMBOANGIITIS OBLITERANS WITH PULSATIONS IN THE PEDAL ARTERIES.

Case.	Age.	*Pulsations. Right. Popliteal.	Right. Dorsalis pedis.	Right. Posterior tibial.	Left. Popliteal.	Left. Dorsalis pedis.	Left. Posterior tibial.	Symptoms.	†Circulatory-efficiency test.	Specimen examined.	Trophic changes when admitted.
1	46	4	4	4	4	4	4	Superficial phlebitis. Cold feet. Recurrent periods of cyanosis with pain in the left third and right second toes.	Positive	Second right toe	Partial gangrene of second and third right toes.
2	37	4	4	4	4	4	4	Partial gangrene of fourth left and second right toes. Exercise pain in right arch. Cold feet.	Positive	Second right toe	Trophic changes of nails of the right foot.
3	40	4	4	4	4	0	0	Gangrene of second toe on right foot. Superficial phlebitis. Exercise pain in both calves	Positive	Second right toe	Gangrenous ulcer on the second toe of right foot.
4	40	4	4	4	1–4	1–4	1–4	Sudden pain and pallor in the first and second toes of the left foot followed by cyanosis and partial gangrene.	Positive	First and second left toes	Dry gangrene of the first and second toes of the left foot.
5	38	3	2	1	2	0–1	0–1	Severe fatigue and mild exercise pain in arch. Ulcer of second toe on right foot. Slowly progressive gangrene on second toe of the left foot.	Positive	Arteries of left leg	Gangrenous ulcer on the second left toe.
6	33	1	0–2	1	2	0	1	Bluish discoloration of several toes with pain. Amputation for relief. Exercise pain in arch. Intermittent bluish discoloration of second and third toes of right foot.	Positive	Second and third right toes	Partial gangrene of the second and third toes of the right foot.
7	22	0	2	0	0	0	0	Progressive exercise pain in both calves.	Positive	Arteries of right leg	Partial gangrene of right first toe and ulcers between toes of right foot.
8	39	4	2	4	4	0–2	4	Bilateral arch fatigue. Progressive exercise pain in right arch and calf. Abnormal fatigue in the left calf.	Positive	Arteries of right leg	Thickening of the skin over the weight-bearing areas.

* Graded from 4 to 0. 4 denotes normal pulsation. O denotes absent pulsation.
† Positive if there is abnormal pallor when the feet are elevated or abnormal rubor when they are dependent.

CASE II.—*Thromboangiitis obliterans distal to the point of normally pulsating arteries of the foot: Amputation of toe with healing.* A man, aged thirty-seven years, a metallurgist, entered the Mayo Clinic May 25, 1926, complaining of pain in the right arch with exercise. Eight months previously a small ulcer had appeared spontaneously on the dorsal surface of the second toe of the right foot. It grew larger, and a similar lesion appeared on the dorsum of the fourth toe of the left foot but healed with local treatment. Roentgen ray treatment, hot packs, and irrigations with Dakin's solution did not change the course of the ulcer on the second right toe, which became extremely painful following the sudden onset of bluish discoloration of the entire toe. The toe was amputated elsewhere and healing was uneventful, but severe pain occurred in the right arch, brought on by exercise and relieved by rest. There never has been superficial phlebitis, or excessive calf fatigue.

All the arteries of the upper and lower extremities pulsated normally (tabulation). The toes of both feet showed Pallor II when elevated and Rubor II when dependent. In the dependent position the rubor of the right foot extended to the ankle. The scar from the amputation was normal. Laboratory data were not significant.

A diagnosis was made of thromboangiitis obliterans of the vessels of the foot distal to the point of normal pulsation. A section of the amputated toe furnished through the kindness of Dr. P. R. Suber, of Pittsburgh, showed almost complete occlusion of the artery by a mass of tissue containing a moderate number of fibroblasts. There was little cellular infiltration. Newly-formed vessels were present in the surrounding tissue (Fig. 2). The occluding mass was thought to be proliferated intima although the possibility of a symmetrically canalized organized thrombus could not be excluded. The proliferated intima is often thought to be an early pathologic change of thromboangiitis obliterans.[5]

Comment. In this case it was necessary to differentiate simple arterial embolism, Raynaud's disease, arteriosclerosis, and thromboangiitis obliterans. The presence of pulsations in the pedal vessels argued for a vasospastic disturbance with gangrene but was excluded by the absence of visible vasomotor disturbances and the sex and age of the patient. The absence of any demonstrable locus for emboli and the bilateral occlusion occurring separately would tend to eliminate simple arterial embolism. Arteriosclerosis was excluded by the age of the patient, and the lack of demonstrable arteriosclerotic changes peripherally on roentgenographic examination. The ocular fundi and central nervous system showed no evidence of arteriosclerosis. The clinical diagnosis of thromboangiitis obliterans was made on the positive circulatory-efficiency test of the distal portion of the foot, the occurrence of spontaneous nonhealing ulcers, the sudden bluish discoloration of the toe associated with severe pain, and the occurrence of intermittent pain in the arch. Microscopic data confirmed the diagnosis. The later development of arch claudication indicated progression of the lesion to a higher level.

CASE III.—*Thromboangiitis obliterans distal to the point of normal pulsations in the arteries of the foot: Successful amputation of a toe.* A man, aged forty-nine years, came to the Mayo Clinic January 2, 1925, because of sore feet and discoloration of the tip of the second toe of the right foot.

Ten years previously he had noticed intermittent pain in the calves with exercise. This lasted for one month and then disappeared for five years. At the end of another year following chilling of the feet the soles became sore and the calves painful; the latter was worse at night and was independent of exercise. The next year the soles of the feet became sore and very cold suddenly, but no change in color was noticed. In the autumn of the following year the feet and calves became sore and the soreness continued through the winter. In the spring all symptoms disappeared. Again in the later summer persistent aching began in the calves, and in the winter became so severe as to interfere with sleep and ordinary daily routine. The pain was progressive. Four months before the patient's visit to the Clinic most of the pain was localized in the right leg and foot, and was sharp, stinging and throbbing. For six weeks he had been unable to sleep without hanging the right leg out of bed. For the last two years there had been numbness, swelling, and aching, and pain in both hands. During the same period there had been recurrent superficial phlebitis over the legs, thighs and arms. Three weeks before admittance a cow had stepped on the right foot and injured the second toe slightly. Severe pain followed. A blood blister appeared and was opened by the patient. The tip of the toe became gangrenous. An ulcer followed and persisted. In the last year he had lost 20 pounds in weight.

The patient was moderately emaciated. The tonsils were enlarged and septic. Pyorrhea was marked. Both feet were cold, cyanotic, and perspiring. The skin and nails of the toes of the left foot were thick and rough. The second toe of the right foot was gangrenous and there was edema III extending to the ankle. The skin of the right foot was tense, shiny, and red. The main arteries of the left arm and the right foot and leg were pulsating normally (tabulation). The dorsalis pedis and posterior tibial arteries of the left foot were pulseless. The left foot when elevated showed Pallor III, and Rubor II when dependent. The right foot when elevated showed Pallor III, and when dependent Rubor II and cyanosis. The right radial artery showed diminished pulsation. The Wassermann reaction on the blood was negative. The blood was normal chemically and cytologically. Renal function and the urine were normal. The roentgenogram showed periapical infection in two teeth. The arteries of the legs were not visible by the Roentgen ray. The systolic blood pressure was 130, the diastolic 80. A diagnosis was made of thromboangiitis obliterans of both feet with gangrene of the second toe of the right foot.

Sodium citrate was given intravenously and alcohol dressings and heat applied locally. Gangrene and pain progressed in the second toe of the right foot and it was amputated at the proximal joint. Seventy-two days after the patient's admittance he was dismissed from observation free from pain and with a well-healed amputation stump. One year later he was free from symptoms, except slight aching in the feet in cold weather.

Microscopic study showed that the arteries of the toes were partially occluded by an organized thrombus. Marked canalization was present. There was but little cellular infiltration to indicate an old lesion (Fig. 3).

Comment. Thromboangiitis obliterans was manifested by the presence of superficial phlebitis, the absence of demonstrable arteriosclerosis, and symptoms of vascular occlusion and obliteration of the arteries in the opposite extremity. The normal pulsations in the vessels of the foot with the gangrenous toe indicated an obliterative process distal to the point of palpation of the main arteries of the extremities. The diminished pulsation in the right radial artery showed that the process existed in this vessel.

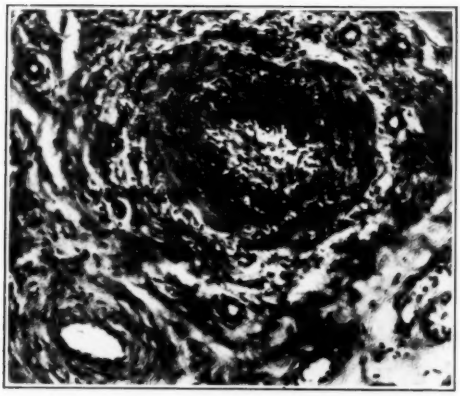

FIG. 1.—An artery from a toe in a case of thromboangiitis obliterans with normally pulsating arteries of the feet. There is complete obliteration of the lumen with a connective-tissue mass moderately infiltrated with leukocytes.

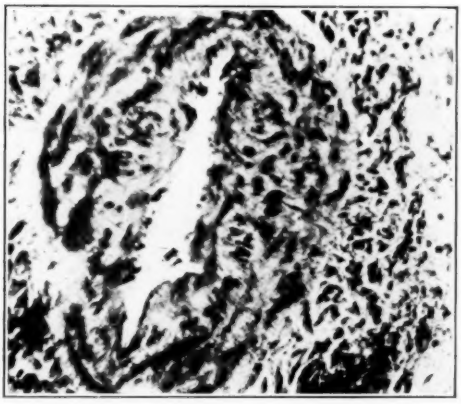

FIG. 2.—An artery from a toe of a case of Buerger's disease with normally pulsating arteries of the feet. Note the marked narrowing of the lumen by the proliferated intima or a symmetrically canalized thrombus and the newly-formed arteries in the surrounding tissue.

FIG. 3.—Section of an artery of a toe from a case of Buerger's disease with normally pulsating arteries of the feet. The lumen is partially occluded by a thrombus which is markedly canalized.

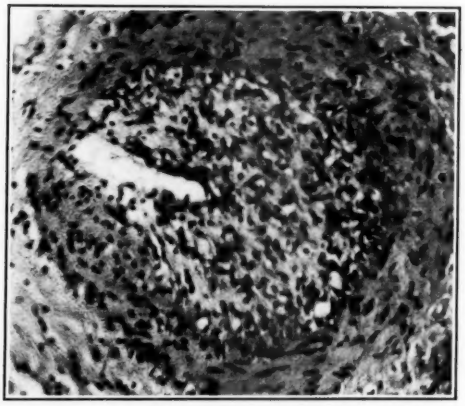

FIG. 4.—Artery from a toe in a case of Buerger's disease with normally pulsating arteries of the feet. Note the almost complete vascular occlusion.

CASE IV.—*Thromboangiitis obliterans distal to the point of normal pulsations in the arteries of the foot: Successful amputation of toes.* A Jewish peddler, aged forty years, came to the Mayo Clinic June 28, 1926, complaining of "foot trouble." There had been no symptoms in the extremities referable to vascular disease until fifteen days before admittance when spontaneous pain appeared in the right great and second toes. On inspection the toes were white and cold but normal color returned following the application of heat. Two hours later severe pain developed in the distal half of the foot which became white and bloodless. Following the application of heat the normal color and warmth returned to all the foot except the left first and second toes which remained cold and white until two days later when a bluish discoloration appeared over the tip of the first toe and to a lesser degree over the second toe. The discoloration slowly progressed and the pain became severe.

On examination pyorrhea, enlarged infected tonsils, bilateral inguinal hernia, and moderate generalized adenopathy were noted. The upper and right lower extremities showed nothing abnormal. There was no evidence of sclerosis of the peripheral vessels. There was dry gangrene of the distal phalanx of the first toe of the left foot and marked discoloration of the tip of the second toe. When dependent the tips of the toes showed Rubor I to II, and when elevated Pallor I. The pulsation of the dorsalis pedis and posterior tibial arteries varied from normal to barely palpable. The blood count and urinalysis showed nothing abnormal. The function of the kidney was normal and the vessels of the legs could not be seen in the roentgenograms. The diagnosis was acute occlusion of the arteries of the first and second toes of the left foot, probably due to thromboangiitis obliterans. The first and second toes were amputated and uneventful healing followed. Microscopic examination of the tissues showed arterial occlusion by a fibrous-tissue mass containing many fibroblasts and a few leukocytes. Partial canalization was present. There were no newly-formed vessels in the surrounding tissue (Fig. 4).

Comment. The sudden onset of pain and pallor indicated vascular occlusion. If this is present in the foot it is probably due to reflex spasm of the larger arteries which is initiated by the sudden occlusion in the vessels of the toe. Sudden vascular occlusion without trauma occurs as the result of simple embolism or thrombosis; the latter occurs frequently as an early lesion in arteriosclerosis or thromboangiitis obliterans. The age and nationality of the patient and the absence of any demonstrable arteriosclerosis made the diagnosis of thromboangiitis obliterans tenable. This diagnosis was verified microscopically. Raynaud's disease was excluded by the asymmetry of the disturbance, the sex of the patient, and the absence of definite color changes of the Raynaud type in the extremities.

CASE V.—The arteries of the amputated leg in this case were partially occluded by an organized thrombus with moderate cellular infiltration. There was moderate canalization and a small artery had formed within the thrombus. Moderate vascularization was present in the media and in the surrounding tissue.

CASE VI.—The arteries of the amputated toe were completely occluded and there had been an attempt at canalization. Cellular infiltration was slight and there was no evidence of increased vascularization in the media or surrounding tissue.

CASE VII.—The arteries of the leg were obstructed by an organized thrombus. Moderate canalization of the thrombus was present and there was marked leukocytic infiltration, probably indicating a recent inflammatory process superimposed on the older obstructing lesion.

CASE VIII.—The lumen of the artery was occluded by an organized thrombus which was moderately infiltrated by leukocytes. Canalization had occurred and an increased number of small bloodvessels were present in the media and in the surrounding tissue.

Discussion. The group represented by Cases V, VI, VII and VIII, in which pulsations were diminished in the palpable arteries of the feet needs no particular comment. Sufficient signs and symptoms of vascular occlusion were present to establish the diagnosis provided one was aware that complete obliteration of the usual palpable vessels is not essential. The differential diagnosis of Buerger's disease and arteriosclerotic disease depends on the patient's age, sex, and nationality, the presence or absence of venous involvement (superficial or deep) the presence or absence of arteriosclerosis elsewhere (radial arteries, or ocular fundi) or the roentgenographic demonstration of arteriosclerosis in the affected extremity. There is a group of patients, of more than forty-five years of age who are suffering from thromboangiitis obliterans, in which medial calcification in the peripheral arteries is demonstrable and indicates a mixed lesion.

In the group of patients with normally pulsating arteries of the feet (Cases I, II III and IV) a more or less definite clinical syndrome exists. The patients have been, as a rule, entirely free from symptoms in the affected extremity although the disease may have pursued its usual course in the other extremities (Case III). The onset is sudden with spontaneous pain and pallor in one or more toes or the distal half of the foot. Warming only partly restores the normal color of the tissue, although in some instances there is complete return to normal for a short time. Gradually the bluish discoloration increases and recovery is successively less complete. The pain increases and amputation is necessary. The frank gangrene or gangrenous ulcers of the type occurring when vascular obliteration is more extensive do not occur, since amputation is necessary for relief of the pain before this stage is reached. Healing is uneventful, owing to the adequate circulation proximal to the toes. Other toes may later be similarly affected. On examination the toes are cold, discolored, and tender. The palpable arteries of the feet pulsate normally and the skin proximal to the toes is normal. There is moderate rubor, usually of all the toes when in the dependent position, and moderate blanching with elevation. The diagnosis of vascular occlusion of the toes is made without difficulty. Simple embolism must be excluded. The differential diagnosis of arteriosclerotic disease and Buerger's disease rests on the points

discussed. Pathologic proof should be sought in cases in which toes are removed. Raynaud's disease is clinically excluded by the age, sex and race of the patient, the asymmetry of the active disturbance of single toes, the incomplete vasomotor reactions, the occurrence of superficial phlebitis, the pallor induced in the toes with elevation, and the rubor when they are in the dependent position.

In all probability the vascular disease has been present in the toes previously, but the gradual obliterative process in the lumen of the arteries has been insufficient to cause symptoms. The onset of symptoms is the result of sudden thrombosis inducing acute vascular obliteration. This is similar to the obliteration which occurs frequently in larger arteries.

Summary. In approximately 5 per cent of the cases of thromboangiitis obliterans (Buerger's disease) seen at the Mayo Clinic, the pulsations of the dorsalis pedis and posterior tibial arteries were normal. The occluding vascular lesion involved the digital and interosseous arteries or extended into the plantar, metatarsal or tarsal arteries. The signs of vascular obliteration were confined to the distal part of the foot and toes. Because of cyanosis or other color changes and normally pulsating arteries, Raynaud's disease was the usual diagnosis before admission. Cases reported in the male as Raynaud's disease with demonstrable changes in the small arteries are probably most frequently cases of thromboangiitis obliterans, similar to Cases I, II, III and IV described in this paper. All the accessible arteries of the extremities should be carefully palpated as a routine, as occlusion frequently occurs in other extremities and thus furnishes a clue as to the nature of the disease.

Four cases presenting typical symptoms of thromboangiitis obliterans distal to area of the normally pulsating pedal arteries are presented with pathologic data. The recognition of this group is important in order that prophylactic or therapeutic measures may be instituted. Lumbar sympathetic ganglionectomy will produce less vasodilatation[3] and be of less therapeutic value in this type of case than in Raynaud's disease.

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THE BLOOD SEDIMENTATION TEST IN NORMAL MEN AND WOMEN.

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During the summer of 1926 the author was engaged in laboratory work at the Glen Lake Sanatorium. Interest in the sedimentation test was aroused by Cutler's[1] article on the graphic presentation of the results in pulmonary tuberculous patients. It was planned to carry out the test by Cutler's method on some of the patients in the sanatorium, after first trying it on the staff doctors, nurses, dietitians and other employees. Cutler stated that the sedimentation index (total sedimentation of the red blood cells at the end of sixty minutes, expressed in millimeters) for men varies from 2 to 8, with an average of 3 to 4; for health women it varies from 2 to 10 mm., with an average of 5 to 6, and "during menstruation it is probably as high as 12 mm."

In performing the preliminary tests on employees records were kept of the menstrual periods of all the women. Ninety-one women were tested. Of this number, 21 were menstruating at the time of the test and 70 were not. It was found on averaging the results that the average index for those menstruating was 6.4 mm., while for those who were not it was 7.6 mm. This demanded a further study of the question.

In attempting to secure further information regarding this point, it was found that Linzenmeier[2] stated that in normal women five to six hours was the time required for the sedimenting cells to reach the 18-mm. mark. During the menstrual period the time was found to be decreased to three hours. He[3] stated that he always found a more rapid fall during the menstrual period than after it. This difference ranged between one and two hours. He did not mention the number of cases studied, nor the number of observations made on any one case.

Nees[4] stated that in adult women the time required to reach the 24-mm. mark is from thirteen to sixteen hours. During the menstrual period the time decreases to ten hours.

Stemmler[5] stated that the sedimentation time in women was from one hundred to four hundred and fifty minutes. He differed from the authors before quoted in believing that the menstrual periods of healthy women have no effect on the sedimentation time.

It appeared that the question was not definitely settled. Since pregnancy itself does not alter the sedimentation test before the third or fourth month, as found by Fahraeus,[6] Linzenmeier,[7] Friedländer,[8] Alexander,[9] Baer[10] and Bochner,[11] it was difficult to

see why the menstrual period should produce a change in it. The question of a possible variation in the test in men, from time to time, arose.

It seemed advisable to carry out a series of tests on normal men and women over a period of several weeks. When the University opened in the fall, and the author's work was resumed there, a call for volunteer men and women was given. Thirteen men and 18 women responded, and their consent to act as experimental subjects has made the work possible. The subjects were all University students, in good health, ranging from eighteen to thirty-four years of age.

TABLE I.—SEDIMENTATION RATES IN NORMAL MALES.

Name.	Observation.		1 hr.	2 hrs.	8 hrs.	18 hrs.	24 hrs.
			Mm.	Mm.	Mm.	Mm.	Mm.
M. A.	9 wks.	Minimum	1.0	6.0	13.0	16.0	17.0
		Maximum	6.0	13.0	19.0	21.0	23.0
		Average of 3	3.0	7.3	15.3	18.3	20.0
E. C.	7 wks.	Minimum	0	1.0	7.0	13.0	14.0
		Maximum	2.0	4.0	11.0	17.0	19.0
		Average of 4	0.7	2.2	9.0	14.2	15.5
A. G.	9 wks.	Minimum	1.0	2.0	9.0	14.0	15.0
		Maximum	2.0	3.0	12.0	17.0	19.0
		Average of 3	1.3	2.6	10.3	15.3	17.3
E. G.	7 wks.	Minimum	1.0	3.0	12.0	16.0	17.0
		Maximum	5.0	11.0	18.0	21.0	22.0
		Average of 6	2.3	5.7	13.6	18.0	19.2
S. E. H.	6 wks.	Minimum	1.0	3.0	12.0	15.0	18.0
		Maximum	3.0	6.0	16.0	19.0	21.0
		Average of 7	2.0	4.4	14.0	17.0	19.4
H. K.	6 wks.	Minimum	0	2.0	8.0	12.0	12.0
		Maximum	1.0	3.0	10.0	16.0	17.0
		Average of 7	0.6	2.1	8.8	14.2	15.2
A. D. K.	5 wks.	Minimum	1.0	4.0	11.0	17.0	18.0
		Maximum	2.0	5.0	14.0	19.0	21.0
		Average of 4	1.2	4.5	12.7	18.0	19.2
A. L.	9 wks.	Minimum	0	1.0	6.0	11.0	13.0
		Maximum	4.0	9.0	18.0	20.0	24.0
		Average of 3	1.6	4.0	12.0	15.5	17.3
	(Submucous resection, 3 weeks before maximum results)						
G. E. L.	5 wks.	Minimum	2.0	5.0	13.0	17.0	18.0
		Maximum	3.0	6.0	15.0	20.0	21.0
		Average of 5	2.4	5.6	14.2	18.5	20.0
E. L.	7 wks.	Minimum	0	1.0	6.0	12.0	13.0
		Maximum	3.0	7.0	10.0	15.0	16.0
		Average of 4	1.0	3.0	8.3	13.7	15.0
J. G. M.	7 wks.	Minimum	1.0	3.0	11.0	16.0	17.0
		Maximum	2.0	5.0	15.0	18.0	19.0
		Average of 6	1.3	4.2	13.0	17.0	18.2
N. P. P.	6 wks.	Minimum	6.0	11.0	18.0	21.0	21.0
		Maximum (cold)	10.0	16.0	23.0	24.0	24.0
		Average of 6	7.7	13.3	20.2	21.8	22.7
M. R. W.	7 wks.	Minimum	1.0	2.0	11.0	15.0	15.0
		Maximum	2.0	5.0	13.0	16.0	18.0
		Average of 6	1.3	3.5	11.4	15.4	16.5

Cutler's method was followed in general, although the readings were taken at greater intervals than he advised for tuberculous

patients. The blood was drawn just before luncheon, in practically every case, and the readings were started soon after the blood was drawn. Since different authors have used different methods, the one-, two-, eight-, eighteen- and twenty-four-hour readings will be given, as this will allow better comparison with the earlier results.

The results found from the studies on the men will be presented first. In order to conserve space, the minimum, maximum and average readings will be given for each time interval.

The results of the test in women are next presented. The minimum and maximum readings between menstrual periods (controls) and the readings during the periods will be given:

TABLE II.—SEDIMENTATION RATES IN WOMEN.

Name.	Period.		1 hr.	2 hrs.	8 hrs.	18 hrs.	24 hrs.
			Mm.	Mm.	Mm.	Mm.	Mm.
J. B.	7 wks.	Minimum	4	9	20	21	22
		Maximum	10	17	25	27	28
		3d day of Period I	7	13	25	26	26
		3d day of Period II	8	14	22	25	25
	(7-day periods; 6 control tests and 2 during periods)						
S. B.	6 wks.	Minimum	7	13	23	24	24
		Maximum	11	18	23	25	25
		3d day of Period I	11	17	23	24	25
		1st day of Period II	8	15	22	24	24
	(4-day periods; 4 control tests and 2 during periods)						
L. C.	6 wks.	Minimum	2	5	16	18	18
		Maximum (cold)	7	13	20	23	23
		1st day of Period I	2	5	14	17	18
		2d day of Period II	5	9	18	21	21
	(3-day periods; 5 control tests and 2 during periods)						
I. F.	9 wks.	Minimum	2	6	16	19	19
		Maximum	4	9	18	21	21
		1st day of Period I	3	7	17	21	22
	(5-day periods; 6 control tests and 1 during period)						
M. W. F.	6 wks.	Minimum	1	3	13	17	18
		Maximum	2	6	15	21	22
		2d day of Period I	1	2	14	19	21
		3d day of Period II	1	3	14	19	21
	(5-day periods; 4 control tests and 2 during periods)						
V. F.	5 wks.	Minimum	3	6	17	19	20
		Maximum	4	10	18	21	21
		1st day of Period I	4	9	17	20	21
		4th day of Period II	4	7	16	19	19
	(6-day periods; 4 control tests and 2 during periods)						
E. M. G.	21 wks.	Minimum	6	12	21	23	24
		Maximum	9	15	24	26	27
		2d day of Period I	7	13	24	26	26
		1st day of Period II	6	13	21	24	25
	(2-day periods; 7 control tests and 2 during periods)						
M. H.	8 wks.	Minimum	2	6	14	17	18
		Maximum	6	11	22	24	25
		2d day of Period I	6	11	21	24	25
		1st day of Period II	6	11	20	22	23
	(5-day periods; 4 control tests and 2 during periods)						

TABLE II.—SEDIMENTATION RATES IN WOMEN—(*Continued*).

Name.	Observation.		1 hr.	2 hrs.	8 hrs.	18 hrs.	24 hrs.
B. H.	8 wks.	Minimum	11	18	24	25	25
		Maximum	17	21	25	26	26
		3d day of Period I	13	20	25	27	28
		1st day of Period II	13	20	23	24	24
	(4-day periods; 4 control tests and 2 during periods)						
M. A. J.	9 wks.	Minimum	3	6	17	19	19
		Maximum	6	11	22	23	24
		Irregular periods*					
	(5-day periods; 5 control tests)						
M. J.	9 wks.	Minimum	7	13	21	21	22
		Maximum	11	20	24	25	25
		1st day of Period I	11	17	24	25	25
	(3-day periods; 6 control tests and 1 during period)						
M. L.	10 wks.	Minimum	4	9	20	23	23
		Maximum	5	11	22	24	25
		3d day of Period I	4	10	22	24	25
	(4-day periods; 3 control tests and 1 during period)						
B. M.	16 wks.	Minimum	4	9	16	20	21
		Maximum	5	9	17	20	21
		3d day of Period I	5	10	20	24	25
	(4-day periods; 3 control tests and 1 during period)						
S. O.	8 wks.	Minimum	5	9	19	21	22
		Maximum	7	13	23	24	24
		1st day of Period I	5	11	19	23	25
	(5-day periods; 4 control tests and 1 during period)						
A. R.	5 wks.	Minimum	2	6	18	22	22
		Maximum	5	9	18	23	23
		4th day of Period I	4	8	18	20	21
		1st day of Period II	2	7	16	21	22
	(4-day periods; 3 control tests and 2 during periods)						
G. S.	5 wks.	Minimum	5	11	17	21	22
		Maximum	7	13	20	23	23
		1st day of Period I	4	9	15	21	22
		1st day of Period II	6	11	21	22	23
	(4-day periods; 4 control tests and 2 during periods)						
R. T.	7 wks.	Minimum	1	4	14	17	22
		Maximum†	10	16	20	22	23
		6th day of Period I	4	12	20	21	22
		3d day of Period II	6	12	20	22	23
	(6-day periods; 5 control tests and 2 during periods)						
I. Z.	7 wks.	Minimum	6	9	18	20	20
		Maximum	10	17	24	26	26
		1st day of Period I	7	13	22	24	24
		3d day of Period II	7	12	20	21	22
	(3-day periods; 4 control tests and 2 during periods)						

* None occurred during this study.
† Scarlet inoculation.

It will be noticed from the tables that in every man tested the index varied a few millimeters from time to time. Sixty-four tests were done on the 13 men. Only 1 case, N. P. P., showed an average index above 3 mm. He has a slight nasal infection which may be

responsible for the faster sedimentation rate. Taking into consideration the number of tests on each individual and the reading of each, a general average has been made. The following results were found for the men: One hour, 2.1 mm.; two hours, 4.9 mm.; three hours, 7 mm.; four hours, 8.4 mm.; five hours, 11.1 mm.; eight hours, 12.7 mm.; eighteen hours, 16.8 mm.; twenty-four hours, 18.2 mm. These figures show a slightly slower sedimentation than Cutler's normals.

The tables likewise show a variation in the test in women, regardless of the menstrual periods. The variation is greater among the women than among the men, but in no case examined was a faster rate found during a period than at some time between periods. Eighty-one tests were done on the 18 women between periods. The average for the entire group was found to be: One hour, 5.7 mm.; two hours, 11.1 mm.; three hours, 14 mm.; four hours, 16.1 mm.; eight hours, 20.1 mm.; eighteen hours, 22 mm.; twenty-four hours, 22.7 mm. There is certainly no doubt about the more rapid sedimentation in women. Whether or not there is a difference in fibrinogen contents of the sexes has not been determined by the author as yet and no published results have been found on this point.

There were twenty-nine tests performed during the menstrual periods. The average readings were found to be: One hour, 5.9 mm.; two hours, 11 mm.; eight hours, 19.8 mm.; eighteen hours, 22.6 mm.; twenty-four hours, 23.3 mm. The one-hour reading was found to be 0.2 mm. greater than the one-hour reading during the control periods. This surely is no significant difference. The eighteen-hour and twenty-four-hour readings showed a greater sedimentation during the periods, but even here the difference is less than 1 mm. Since the averages during the periods so nearly coincide with the averages between the periods, the author believes that we are justified in concluding that the menstrual periods in healthy women do not affect the sedimentation rate.

Summary. 1. The sedimentation rate shows some variation from week to week among normal men.

2. The sedimentation rate shows slightly more variation from week to week (exclusive of menstrual periods) among normal women than among men.

3. The averages show that the rate of sedimentation is faster in women than in men.

4. The sedimentation rate during the menstrual periods is not faster than between periods. In every case studied as rapid a rate was found between periods as during the periods.

NOTE,—The author wishes to thank the students who so kindly volunteered to make this possible and those who aided with the venepunctures.

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ADDISON'S DISEASE, SUPRARENALOPATHIES, SCLEROSIS OF THE GLANDS OF INTERNAL SECRETION.

Clinical Reports and Review of the Literature.

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and

Necropsy Findings and Illustrations.

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If a patient presents the classical signs and symptoms of Addison's disease and at autopsy shows bilateral destructive disease of the adrenals, there can be no doubt as to the diagnosis. But if a patient is clinically one of Addison's disease and at autopsy shows no lesions of the adrenals, it is usually assumed that there was destruction or impairment of function of the chromaffin system outside of the suprarenal glands. Such a diagnosis is correct because Addison[1] described a clinical and not a definite pathologic concept.

Addison's disease is a clinical concept, therefore it is most difficult to differentiate between instances of toxic and infectious suprarenalopathies. Time is the only differential factor because the patient soon recovers from the latter. The second case report is in all probability an example of suprarenalopathy.

The third case is reported to show that widespread destruction of the suprarenal glands may be present and that typical symptoms of Addison's disease may be lacking. This instance illustrates the error in calling everything Addison's disease, which at autopsy shows destruction of the suprarenal glands.

Case Reports. Case I.—The first case is clinically and pathologically an instance of Addison's disease. He was a white man, aged thirty-five years, unmarried and an electrician by trade. On August 26, 1926, he was

admitted to the tuberculosis service and later transferred to the medical service. He complained of loss of appetite, weakness, nervousness, "blind staggers," loss of weight and shortness of breath.

The present illness began in the fall of 1925, with weakness and insomnia. He was dizzy when he changed position quickly. A few months later he noticed dyspnea and a loss of weight. In March of 1926 he was forced to limit his activities on account of weakness. The patient said, "Since spring I have eaten less, slept more and grown gradually weaker." During the month of August he was at a summer resort but did not improve. He left the resort to come to the hospital.

He had the usual childhood diseases and in 1912, gonorrhea. Otherwise he had enjoyed good health. The family history was unimportant.

A general physical examination on admission showed a well-developed, undernourished man of thirty-five years, height 72 inches, weight 130 pounds (58.9 kg.), temperature, 98° F.; pulse, 70; respiration, 16; blood pressure, systolic, 84; diastolic, 52 (mm. Hg.). The skin was dry and of good color, except over the exposed surfaces of the body, which was an exaggerated sunburn-brown in color. The genitalia were deeply pigmented. On the mucous membranes of the cheek were two or three brown pigmented spots. The hair was dry, fine and of the male type of distribution. There were no palpable lymph nodes. The thyroid was not enlarged. The pupils were small and reacted to light and during accommodation. The nose, sinuses, teeth and tongue showed nothing unusual. The tonsils had been cleanly removed. Nothing unusual was noted in the heart and lungs. The liver and spleen were palpable; the abdomen was otherwise normal. The rectum, prostate and genitals were not unusual except for partial atrophy of the right testicle. The extremities, reflexes, station and gait were normal. Ophthalmoscopic examination showed clear media and normal fundi except for moderate engorgement of the retinal veins. There was no increase in the retinal pigmentation.

Laboratory studies showed the following: Basal metabolic rate, + 2; Roentgen ray studies of the thorax showed the heart and lungs normal, of the gastrointestinal tract, a spastic colon; red blood cells, 4,200,000; hemoglobin, 90 per cent (Dare); white blood cells, 10,700; with P.N.N. 42 per cent, and lymphocytes 56 per cent; the serology, blood chemistry, urine, feces and sputum showed nothing unusual. There was very little change in the blood counts, urine analysis and blood chemical studies after admission. The last hemoglobin was 80 per cent (Dare).

The unusual feature in this patient's illness was an uncontrollable itching of the skin. At times the itching was severe enough to prevent sleeping.

After transfer to the medical service the Muirhead régime of treatment was begun. The epinephrin was increased until a dosage of 20 minims was given hypodermically four times daily. The desiccated suprarenal was increased until he received 80 gr. by mouth daily. He was on a high carbohydrate diet from the time of admission to the hospital until his death. About one week after beginning the Muirhead régime thyroid extract was begun. The thyroid therapy was continued until he was given 6 gr. daily. About one week later he became nervous and the pulse rate went to over 100 per minute, so the thyroid therapy was discontinued.

The patient's appetite soon became capricious. For several days at a time he could scarcely retain any food on account of nausea and vomiting. During such an attack he would receive glucose (10 per cent solution) to prevent dehydration and supply a little food. When the attack was over, he was comfortable except for the weakness. Near the end he became so weak that he could not raise his hands or draw his feet up in the bed. The emaciation was most extreme. November 18th, he became too weak to talk and at 6 P.M. the blood pressure was 68 (mm. Hg.) systolic, and the diastolic

could not be determined. Toward midnight Kussmaul breathing was observed; at 2 A.M., the 19th, respiration ceased.

Postmortem Findings. General description confirmed the findings noted under physical examination. Emaciation was extreme. The only findings noted in the brain were some granulations in the fissure between the cerebellar lobes. No pathology was noted in the pituitary. Some lymphoid hyperplasia was noted at the base of the tongue and in the pharynx. The thyroid was enlarged; the right lobe measuring 7 x 3 cm. and weighing 18 gm., the left lobe measuring 6 x 2.5 cm. and weighing 21 gm. There was a small adenoma in the right lobe. Microscopically the acini were irregular in size with a tendency to be larger than normal and were filled with colloid. There was no epithelial hypertrophy or hyperplasia. In places fetal tissue was found in the stroma. The thymus was easily identified and consisted chiefly of fat. It measured 6 x 2 x 1 cm. On section some lymphoid tissue and a villous-like epithelial structure was found centrally. Attached to the anterior surface of the trachea and 1 cm. below the thyroid were bilateral lobes of glandular tissue (Fig. 1). The right lobe measured 6 x 1 x $\frac{3}{4}$ cm. and the left 6.5 x 2.5 x 1 cm. This tissue consisted of lobules of lymphoid tissue surrounded by fibrous tissue stroma. Many of these lobules contained clumps of large epithelial cells centrally located with a tendency to be hyalinized.

The heart was small, weighing 185 gm. and the muscle was soft. The mitral valve was sclerotic and probably insufficient. The coronaries and aorta were essentially normal. There were many hypertrophied lymph glands attached to the trachea along its entire length. Those at the bifurcation were deeply pigmented and some were caseated. There were no pleural adhesions to the chest wall but on both sides there were fibrotic adhesions between the lobes. At each apex there were a few small fibrotic scars. The upper portion of the lower right lobe contained a pigmented fibrotic nodule 1 cm. in diameter which was caseous centrally. Sections through this nodule and the lymph glands revealed healed tuberculosis with no evidence of activity.

Nothing abnormal was noted in the gastrointestinal tract. There were many enlarged lymph glands in the mesentery and retroperitoneally which on section consisted of a simple lymphoid hyperplasia with large active germ centers. The liver was negative except for some fibrosis and lymphocytic infiltration around the bile ducts. The cystic duct was obliterated by fibrous tissue. The pancreas appeared approximately normal. Fibrous tissue was considerably increased in the stroma and especially around the ducts. The acini were indistinct and gave the impression of being matted together as if compressed. The islands appeared about normal in number and were free from sclerosis and also appeared somewhat compressed (Fig. 2). The spleen was large and soft due to passive congestion and lymphoid hyperplasia. The kidneys were negative except for passive congestion and a few miliary abscesses in the deep cortex. These lesions did not resemble tuberculosis. The urinary tract was otherwise normal. The genital tract was normal except for an atrophic testicle on the right side which presented nothing unusual microscopically.

The right adrenal was identified with difficulty in an adherent and quite vascular mass of areolar and fatty tissue. Many enlarged lymph glands, some reaching a size of 2 cm., were embedded in this tissue. These glands showed only hyperplasia on section. A flattened adrenal was found in this tissue. It was shrunken in size to an average thickness of less than 2 mm. and a breadth of about 1 cm. On section cortex and medulla could not be definitely differentiated. Microscopically, its structure was quite distorted. Its capsule was thickened fibrous, vascular and composed about 30 per cent, of the total area. The cortical tissue had lost its characteristic structure and

the cells varied in size, some containing large clear vacuoles. No medullary structure could be identified (Fig. 3). A very similar condition was found on the left side. The adrenal was larger, measuring 6 x 1.5 x 0.5 cm. One lobe was 1 mm. thick and undifferentiated. The other was 2 mm. thick and consisted of a thin chocolate-colored periphery with a central gray area. This differentiation was well marked in the middle portion of the gland. The thin portion of the gland was found to be entirely free from gland structure except for a few scattered cells. This tissue was continuous with the capsule of the rest of the gland. It consisted of highly vascular fibrous tissue with considerable diffuse and clumped lymphocytes. This tissue composed about 50 per cent of the thicker lobe. This lobe had some glandular tissue centrally which appeared to be cortical in type rather than medullary. In the thick middle portion of the gland there were some cells centrally which were apparently medullary in type. These cells and the cortical cells showed extensive degenerative changes (Fig. 4).

In summary, a man aged thirty-five years, who after an illness lasting about one year, which was characterized by asthenia (muscular and circulatory), nausea and vomiting, loss of weight, bronzing and itching of the skin, extreme emaciation, died three months after admission to the hospital. Postmortem examination showed an old tuberculosis of the lungs, congestion of the pancreas, enlarged persistent thymus, miliary abscesses in the kidneys, and destructive caseous lesions in the suprarenals.

CASE II.—The second patient is reported to show how closely the Addisonian syndrome may be simulated and how easily it would be to diagnose the patient's condition as Addison's disease and to think a recovery had been observed.

The patient, a white man, unmarried, aged thirty-one years, a plumber by trade, was admitted to the medical service September 9, 1926. He complained of dizziness, pain in the back and right side, weakness, nausea and vomiting.

The present illness began two weeks previous to admission following an attack of "influenza," which confined him to bed for several days. After about a week he began to try to work when his present symptoms appeared. The symptoms did not improve so he came to the hospital.

The patient was at the hospital in October, 1923, at which time a refractive error was corrected by glasses. The refractive error was the only thing of importance in a general physical examination at this time. The blood pressure was systolic, 110; diastolic, 80 (mm. Hg.). The past and family histories were unimportant.

A general physical examination on September 9, 1926, showed a well-developed and somewhat undernourished man of about thirty years, temperature, 99.8° F.; pulse, 60; respiration, 18; blood pressure, systolic, 80; diastolic, 48 (mm. Hg.); height, 66 inches; weight, 132 pounds (60 kg.). The skin was dry, dark, but not abnormally pigmented. The mucous membranes were of good color. The epitrochlear lymph nodes and those in the posterior cervical triangles were palpable. The rectum, genitals, extremities and complete neurological examination revealed nothing of importance.

Laboratory findings showed 5,000,000 red blood cells, 20,000 colorless corpuscles, 79 per cent polymorphonuclear neutrophils and 19 per cent of lymphocytes. The hemoglobin was 90 per cent (Dare). The urine, sputum, feces, gastric analysis and Roentgen ray studies of the heart, lungs and gastrointestinal tract showed nothing unusual. The Kahn test for syphilis was negative.

The patient was put to bed and given a high caloric diet. The nausea and vomiting soon ceased. Three days after admission the white blood

FIG. 1.—Trachea and glands (Case I). Note enlarged thyroid, bilateral lobes of thymus and enlarged lymph glands.

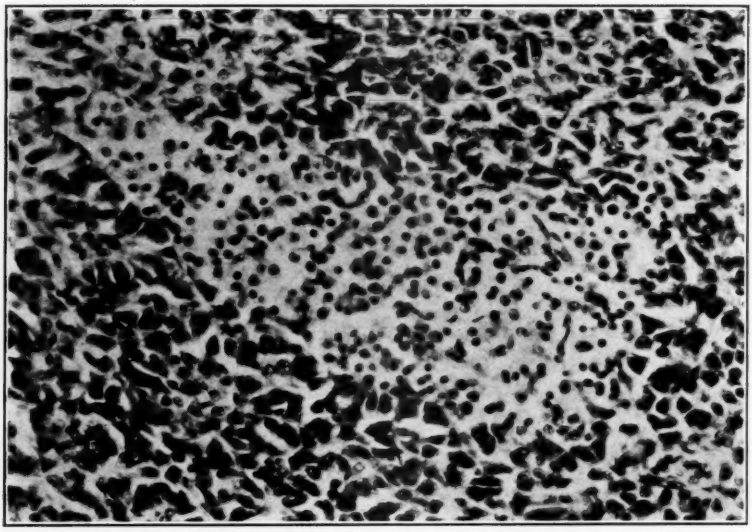


FIG. 2.—Pancreas (Case I) showing large irregular island and irregular arrangement of acini.

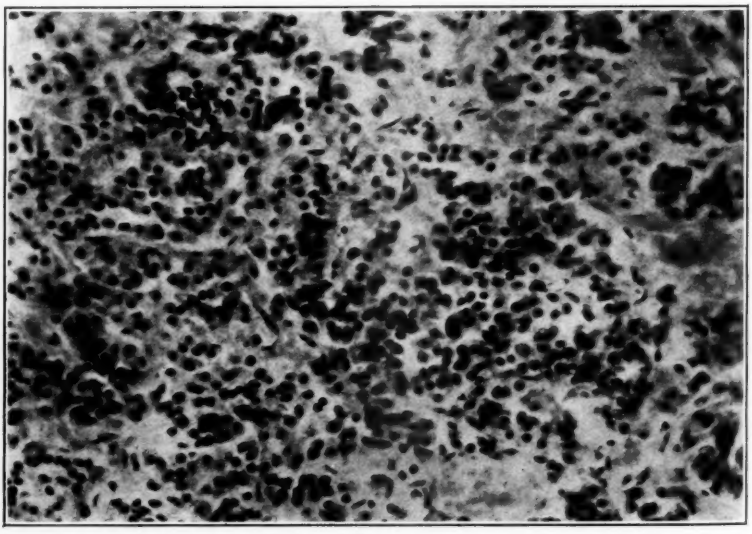


FIG. 3.—Section from adrenal (Case I), showing type of tissue composing capsule and replacing gland.

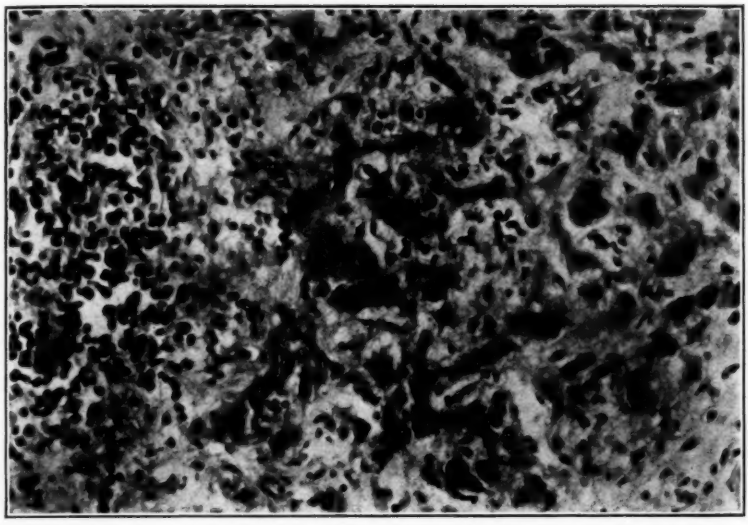


FIG. 4.—Adrenal (Case I) showing degenerated type of cortical cells.

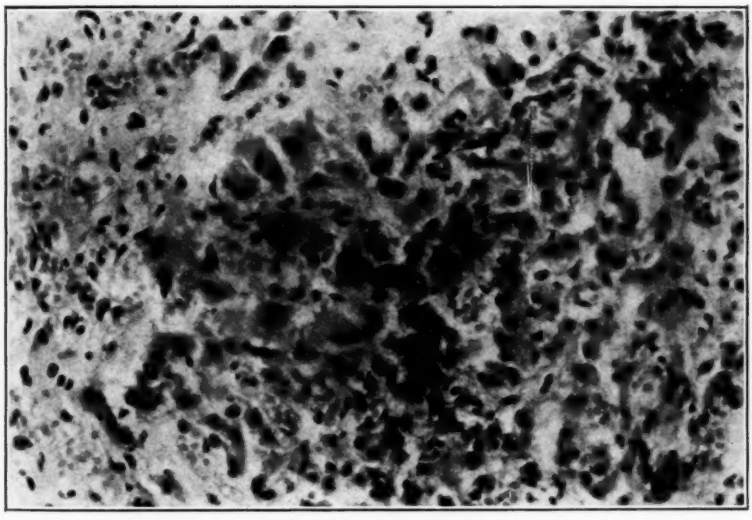


FIG. 5.—Pituitary (Case III) showing vascular congestion and sclerosis.

FIG. 6.—Adrenal (Case III) showing sclerosis, hemorrhage and loss of structural differentiation (low power).

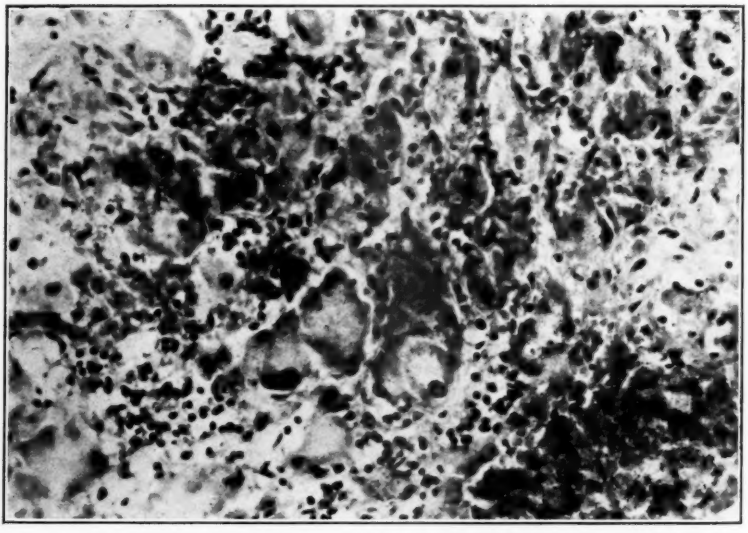


FIG. 7.—Adrenal (Case III) showing cortical cells and hemorrhage (high power).

cell total count was 11,000 with a normal differential count. During this time the temperature returned to, and remained normal. The blood pressure began to increase after about ten days in bed. After a fortnight, the patient was allowed to be up and about the ward. Six weeks after admission he was discharged from the hospital. On the day of discharge the blood pressure was systolic, 106; diastolic, 70 (mm. Hg.).

Since leaving the hospital the patient has been going about his work without difficulty.

In all probability this was an instance of a true toxic or inflammatory suprarenalopathy. There was an infection with an onset and course which simulated influenza. Whether the infection involved the suprarenal glands which caused the symptoms above stated, or whether a toxemia interfered with suprarenal function is a matter of speculation.

Before the World War very little was known about such a syndrome as shown by this patient. The medical profession was so profoundly shocked by Addison's[2] discovery that disease of the small bodies first described by Eustachius[3] in 1563 could produce such spectacular symptoms that it took three-quarters of a century before it could attempt to differentiate various diseases of these glands. This is the reason for the confusion that exists in the literature since all kinds of lesions of the suprarenal glands have been called Addison's disease. The type of case, of which the above patient is an example, is similar to those in the literature which are reported as recoveries from Addison's disease.

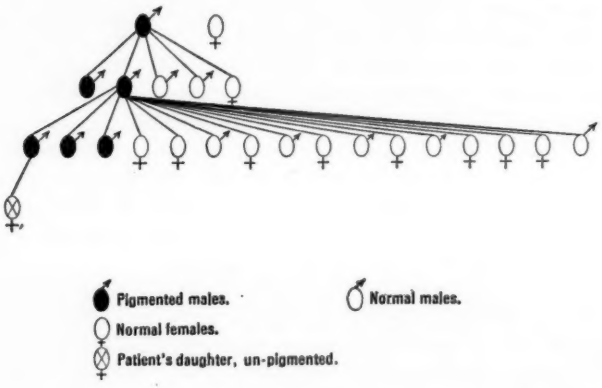
During the past ten years many observations have been made which illustrate the possibility of temporary impairment of suprarenal function. Loeper[4] and others have called attention to symptoms of acute suprarenal insufficiency after typhoid inoculations. Carles[5] has reported instances of War Dyspepsia, which was supposed to be due to suprarenal insufficiency. In 1916 Jousé[6] described a syndrome which he called "Asystolie Surrenale" which produced sudden death. Babes[7] has shown the frequency in which the suprarenal glands are found affected at necropsy. All sorts of toxic and infectious agents have been shown to affect the suprarenal glands and produce low blood pressure and gastrointestinal symptoms, an example of which is the so-called nitritoid reaction following salvarsan administration.

CASE III.—The third case report is not so clear. From the time of admission to the hospital until his death a diagnosis of Addison's disease could not be made. The patient, a white man, aged twenty-eight years, married, a meat inspector, was admitted to the hospital November 20, 1926. He was acutely ill and complained of nausea, vomiting and steady epigastric pain and distress.

The present illness began on November 13, with a feeling of "Just being tired out." That night he slept poorly and the following morning, while at church, he fell asleep, which was unusual for him. During the afternoon he began to have a frontal headache, and at about 11.30 P.M. he was seized

rather suddenly with a chill which lasted for more than an hour. A doctor was called and came about an hour after the chill and told the patient that he had two or three degrees of fever. The chill was followed by nausea, vomiting and severe epigastric pain. The nausea and vomiting continued until admission to the hospital, the pain, however, was not severe after the first day after the chill. The vomitus was light in color and there had been no black stools. The patient had been confined to his bed since the onset of his illness.

In the past the patient had enjoyed fair health. He had measles, mumps, whooping cough, chicken pox and scarlet fever in childhood. There were no other illnesses prior to his entering the Army in 1918. (The report of the Adjutant General of the Army shows that there were no disabilities at the time of his discharge from the Army.) The records of the Veterans' Bureau show that he was suspected of syphilis in 1919 on account of alopecia. Between 1919 and 1921 he was seen by many dermatologists all over the country and every one said that he must have syphilis in spite of the fact



that during this time he had many serologic tests for syphilis reported by many different laboratories as consistently negative. By the end of 1921 the alopecia was complete—not a hair was left on his body. In the latter part of 1921 he had developed a pain in his chest which was worse on the left side over his heart. He was seen by many different clinicians and finally he was sent to Asheville, N. C., for treatment for "pulmonary tuberculosis." The patient had never had weakness, hemoptysis, loss of weight, cough or night sweats. There was no history of any sort of abdominal pain or discomfort.

Since birth there had been a deep brown color of the skin. The patient had 15 brothers and sisters, 8 of whom died in infancy; the others were in good health. The patient's father, grandfather, one uncle (paternal) and 2 brothers had deep bronzing of the skin. There was no history that the bronzing of the skin in any of the above relations was accompanied by cutaneous or subcutaneous nodules. The patient was born in Germany and came to this country while he was quite young, so we know nothing of the family illnesses outside of the immediate family. The patient said that the other members of the family had fair skin and that the pigmented members were jovially termed "black sheep."

The above chart illustrates all that could be learned concerning the familial and hereditary pigmentation.

The general physical examination upon admission showed a well-developed, undernourished, dehydrated man of twenty-eight years, who appeared to be at least forty years of age; temperature, 99° F.; pulse, 100; respiration, 26; blood pressure, systolic, 120; diastolic, 80 (mm. Hg.). The patient was restless and complained of pain in the epigastric region. The eyes were sunken and the conjunctivæ were red and moderately inflamed. There was a total alopecia, the skin was a light bronze color with a somewhat yellow tint, except the areola of the breasts and the genitals, which were as black as those of a negro. There was no evidence of jaundice. The extra ocular movements were correctly performed. The pupils were equal in size, regular in outline and reacted promptly, directly and consensually and during accommodation. There was a severe ulcerative stomatitis, which prevented examination of the throat. There were no palpable lymph nodes. The thyroid gland could not be palpated. The lungs elicited nothing remarkable. The heart was small in outline, M.L. 6 cm., M.R. $2\frac{1}{2}$ cm. The cardiac sounds were just audible and there was a splitting of the pulmonic second sound. There was no evidence of peripheral arteriosclerosis. The abdomen was flat, the liver edge was palpable and there was a diffuse tenderness in the epigastrium, so intense that the spleen could not be palpated. The genitals were normal except for atrophy of the right testicle and the pigmentation. Rectal examination showed nothing unusual. Neurologic and opthalmocoscopic examinations showed nothing remarkable.

Laboratory examinations showed red blood cells, 5,000,000; hemoglobin, 99 per cent (Dare); white blood cells, 12,400; polymorphonuclear neutrophils, 67 per cent. Hemolysis of the red blood cells began at 0.40 and ended at 0.32. The blood chemistry, November 22, was as follows:

Nonprotein nitrogen	112.0	mg. per	100 cc.
Uric acid nitrogen	6.0	"	"
Creatinine	1.5	"	"
Sugar	220.0	"	"
Chlorides	231.0	"	"

The van den Bergh test for bilirubin was normal. The Kahn test for syphilis was negative. The urine was negative for bile acids and pigments, alkapton, melanins, methemoglobin, acetone, diacetic acid and sugar. A trace of albumin and a few granular casts were present. The sputum was negative for tubercle bacilli, Klebs-Löffler bacilli and Vincent's organisms. The feces showed no ova or parasites, and no occult blood, but was positive for hydrobilirubin. Roentgen ray examination of the heart, lungs, stomach and intestines showed nothing unusual except irregularity of the contour of the diaphragm and a spastic colon. After the receipt of the report of the blood chemistry on November 22, 800 cc. of normal saline solution was given intravenously. Blood chemistry on November 23, showed as follows:

Nonprotein nitrogen	90.0	mg. per	100 cc.
Creatinine	1.9	"	"
Sugar	103.0	"	"
Chlorides	430.0	"	"
Plasma CO_2 (volumes per cent)	49.4		

After giving the intravenous saline the nausea and vomiting ceased and the patient was fairly comfortable except for some slight epigastric distress following meals. The temperature remained around 99° F. The total and differential white blood cell counts were normal. There was never any sugar found in the urine. The blood pressure readings were normal except the second day after admission it was systolic, 98; diastolic, 76 (mm. Hg.). Two days before death it was systolic, 118; diastolic, 80 (mm. Hg.).

The patient died very suddenly on the eighth day in the hospital. On the day of his death he said that he had less epigastric distress and a better appetite than he had had since being sick. He sat up in bed and ate his dinner and remained sitting until a few minutes before his death.

Postmortem Findings. General description confirmed the findings noted under physical examination. Brain negative. Sella and pituitary appeared normal grossly (0.75 cm. in diameter). Microscopically the sinuses of the glandular portion were markedly congested and the glandular cells showed irregularity in arrangement and granular and vacuolar degeneration associated with a diffuse fibrosis (Fig. 4). There appeared to be no marked change in the posterior portion. The pharynx and the posterior papillæ of the tongue showed a marked subepithelial lymphoid hypertrophy. The thyroid was grossly normal. Microscopically it presented some congestion and infiltration with lymphocytes. The thymus was not identified. The lungs were normal grossly. The alveolar walls were thickened and there was a tendency to atelectasis and pigmentation. The pericardial cavity was completely obliterated, due to a healed fibrotic process. The heart showed no noteworthy changes. The thickened pericardium consisted of fibrous tissue about 1 mm. in thickness and was practically free from inflammatory infiltration. The coronaries were normal and the aorta was normal except for a few early developing atheromatous patches. The mesentery attained a thickness of 1 cm. in places due to fatty infiltration. Embedded in this fat were numerous firm gray lymph glands of variable size and shape. These glands presented a simple lymphoid hyperplasia. The gastrointestinal tract was normal except for a marked dilatation of the first part of the duodenum. The liver, gall bladder and ducts were not unusual grossly. The sinuses were packed with blood and there was some atrophy and degeneration of cells in the central portion of the lobules. The pancreas was somewhat atrophic and cut with increased resistance. The vessels were congested. The acini appeared about normal. The insular tissue was definitely abnormal, some of the islands being hypertrophic while others were atrophic with slight or no fibrosis. The spleen was somewhat enlarged and the hypertrophic corpuscles could be readily distinguished grossly. The kidneys and urinary tract were somewhat congested. No marked change was noted in the testicle. No adrenal tissue was found on the right side. Fibrotic vessels, identified with reasonable certainty as being adrenal, were attached to some fibrous tissue and a clump of lymph glands. Sections through this tissue revealed a sclerosed artery, fibrous and areolar tissue, and lymphoid tissue. The condition did not appear inflammatory. On the left side a flat quite dark piece of tissue 4 cm. in length was identified as probable adrenal, due to its vascular connection. It was somewhat adherent to the adjacent tissue. It was soft and slate-blue in color, appearing hemorrhagic. Cross-section through this tissue revealed adrenal structure. There was marked atrophy of cortex and medulla, particularly the latter, which appeared to be entirely absent on one side of the lobe. The dark-red discoloration was most conspicuous in this portion of the tissue. Sections revealed marked structural alteration. The lobes averaged less than 1 mm. in thickness. The capsule was fibrotic and had an extensive round-cell infiltration in its deeper layer. Large vessels and arterioles were numerous in this capsule and were packed with blood. The glandular tissue was so degenerated that little normal structure remained. In one lobe apparently only cortical cells remained and they had lost their characteristic form and arrangement. Few of them appeared even approximately normal. They presented all stages of granular degeneration and replacement by fat and lipoid material. In the other lobe similar cortical tissue persisted only as a cap of tissue covering the tip of the lobe. Tissue which appeared to be medullary in type filled in a space

of 4 mm. between these two remnants. It was 1 mm. thick and free from cortex. Extensive degenerative changes were associated with fatty and lipoid deposits. The adrenal structure was further altered by a marked vascular congestion, free blood in the tissue and a fairly marked fibrous tissue and lymphocytic infiltration (Figs. 5 and 6).

In summary, a man of twenty-eight years, who had a familial and congenital pigmentation of the skin, alopecia totalis, a short illness which was ushered in as an acute infection and ended very suddenly not unlike Addison's disease. Autopsy showed absence of one suprarenal and a sclerosis of the remaining suprarenal, pancreas, pituitary and testes, adhesive pericarditis and a general internal lymph node adenopathy. The suprarenal present showed two types of lesions, an acute process which was superimposed upon an old sclerosis. The old sclerotic process had evidently destroyed one gland entirely. The pericarditis is suggestive—did the patient at some time in the past have a generalized infection which caused the pericarditis and started the trouble in the suprarenals and other endocrine glands?

The patient's condition appeared to be one of hereditary pigmentation which is something like an incomplete form of von Recklinghausen's disease. A differential diagnosis includes the following: Chronic and malignant disease of the peritoneum, acanthosis nigricans, chronic gastric and gall bladder diseases, ochronosis, chronic pulmonary disease, malarial melanemia, melanotic sarcoma, exophthalmic goiter, rheumatoid arthritis, argyria, arsenic, vagabonds' disease, syphilis and pellagra. The possibility of admixture with negro blood cannot be ruled out except by history and there was no such history obtainable.

The question arises: Is this an instance of hemochromatosis or the so-called bronzed diabetes which was described by von Recklinghausen[8] in 1889? It was thought, until the patient's death, that hemochromatosis superimposed perhaps upon an incomplete form of von Recklinghausen's disease was the most likely diagnosis.

Hemochromatosis is rare; according to Sprunt,[9] less than 100 cases have been reported. It is characterized by: bronzing of the skin, deposition of iron containing pigments in many organs of the body and cirrhosis of the liver and pancreas. The onset is not unlike diabetes mellitus in many instances. The necropsy findings exclude this diagnosis as there was no pigmentation of the liver, spleen, pancreas, lymph nodes or any other organs of the body. The pigmentation of the skin was both hereditary and congenital. The alopecia, which began in 1918 and ended in 1922, the pituitary, testicular atrophies and the mode of exitus are not characteristic of hemochromatosis.

The alopecia totalis is the first clinical symptom which can be associated with the pathology. Such an alopecia may be either congenital or acquired. As has been stated, the alopecia was acquired and the pathological findings make it unnecessary to

consider the following in a differential diagnosis: Alopecia areata, syphilis, typhoid fever,[10] scarlet fever,[11] fright[12] and various fungus and parasitic infestations. The growth, the distribution and the maintenance of the hair is controlled by the endocrine glands, therefore the alopecia in this case can be accounted for on this basis.

To correlate the onset, course and termination of the patient's last illness with the pathology would be entirely speculative. The gastrointestinal symptoms and the mode of exitus were not inconsistent with the suprarenal pathology, but there was no asthenia either muscular or circulatory.

Sudden death is commonly seen in Addison's disease. The right suprarenal in this patient was so atrophic that it could be located only by following the atrophic suprarenal vessels. This illustrates the extent to which the suprarenals may be destroyed and the blood pressure remain normal. Whether the chromaffin system outside the adrenals was involved we did not know enough, at the time, to investigate. This patient died of a sclerosis and degeneration of the suprarenals, pancreas, testes and pituitary glands, the lesions in the suprarenal being the most advanced.

In most of the instances of sclerosis of the glands of internal secretion which have been recorded, the symptomatology is obscured by concurrent disease. The symptomatology depends upon the gland or glands which are the most profoundly affected. The lesions in the glands involved are practically constant. A brief review of instances with pathologic examinations will illustrate the varied clinical manifestations. Zodek[13] observed several cases which at autopsy showed a connective-tissue diathesis of the glands of internal secretion. He divides the clinical manifestations into two groups: those with obesity, cachexia and low metabolic figures, and those with high metabolic figures. Schick and Wagner's[14] cases showed extreme atrophy of the thymus, thyroid, suprarenals and pancreas, but the clinical picture is not clear on account of the evidences of concurrent food deficiency disease. Hochstetter's[15] case of a farmer, aged thirty-eight years, at the onset of his illness is mixed up with various intercurrent diseases. The illness began with thirst, sleeplessness, headaches, impotence which, after four years, was followed by pains suggesting polyneuritis, weakness, apathy, emaciation and low blood pressure. In the first part of his illness he suffered also with bronchitis and emphysema. At autopsy the thyroid, parathyroids, pituitary and testes were sclerotic. Hirsch's[16] case had syphilis and carcinoma of the esophagus as well as the pathology found in the glands of internal secretion. Blazer and Barthélemy[17] have reported an instance of total alopecia in a man aged forty-one years at the time of death. The alopecia began, without apparent cause, two years before death. At autopsy there was a tuberculous pneumonia, obliterative pericarditis and advanced tuberculosis of the suprarenal capsules.

The following is a short review of the history, etiology, laboratory features, prognosis and treatment of Addison's disease.

History. The oldest record of an illness which in all probability was one of Addison's disease is reported by Manañón.[18] This writer found an account of the illness of a young priest which was reported and recorded in the "Historia primitivia y exacto monasterio del Escorial." The priest's illness occurred in 1554–1557 and dates from fright during a storm when lightning struck the monastery. The illness was one of melancholia, emotional instability, and the white color of the skin changed to a sad pallor. The patient lingered along, from bad to worse, and finally died after an illness which lasted three years.

Addison's monograph in 1855 was a contribution to both internal medicine and endocrinology. It was a stepping stone in the elucidation of Claude Bernard's[19] work on the doctrine of internal secretions which was begun in 1848. Brown-Sequard,[20] stimulated by Addison's observations, began his work on internal secretions by excisions of the suprarenal glands of animals in 1856 and produced fatal symptoms of exaggerated Addison's disease. It was not until 1894 that Oliver and Schäfer[21] discovered that injections of a watery suprarenal extract into the blood of an animal produced slowing of the heart rate and a rise in blood pressure. Abel's[22] isolation of epinephrin in 1896 gave new hope for the treatment of this disease.

Addison's discovery was very slow to take a permanent place in medical literature. It is to the efforts of Sir S. Wilks,[23] who carefully went over the records of Guy's Hospital and picked out many instances of the disease, that we are deeply indebted for its general recognition. It was Trousseau's suggestion to name the disease "Addison's Disease," which name it now bears in all languages.

Etiology. Discussion of the etiology of this disease has always been largely speculative. We know that animals die after the removal of the suprarenal bodies with a certain set of symptoms. The hypotension and asthenia can be accounted for by the lesions of the suprarenals found in most cases. Up to the present time there is no theory that accounts for all the signs and symptoms we see in the disease. The cause of the pigmentation when present is yet unknown.

To account for all the findings in this disease, in all instances, one is forced to assume that there must be an anatomic and functional weakness of the entire chromaffin system which perhaps in most instances is a congenital anomaly.[24] Wiesel[25] demonstrated an entire absence of part of the chromaffin system in a patient who died of Addison's disease, but who at autopsy showed no lesions of the suprarenal glands. This same observer reported another instance in which he found advanced tuberculosis of the suprarenals which was not accompanied by symptoms of Addison's disease, but he was able to demonstrate excessive amounts of chromaffin tissue outside the suprarenals.

In 1895, Star[26] called attention to the frequent association of persistent thymus in Addison's disease.

There are certain etiologic factors which may be mentioned: tuberculosis of the suprarenals is the most common finding at autopsy; rarely nervous excitement,[18] malignancy, pressure on the suprarenal veins,[2] syphilis,[27] lymphadenoma[2] and mycosis fungoides[22] have been recorded. The disease is usually stated to be more frequent in males in the fourth decade of life. Dezirot[29] has collected 48 cases in individuals under sixteen years of age which he thought were Addison's disease. Spencer[30] found suprarenal hemorrhages in 25 out of 105 stillborn babies.

Finkelstein has studied what she considered Addison's disease in children, which is very rare.

Laboratory Features.—The laboratory features of this disease are not unusual. Addison thought anemia was a constant feature of the disease. Averbeck[31] thought than an anemia was present with a reduction of the total volume of blood. Buhl[32] stated that there was a sharp decrease in the total number of blood cells. Tschirkoff[33] observed in 2 patients a daily fluctuation of the whole amount of hemoglobin as well as the relative proportion of oxyhemoglobin to reduced hemoglobin. Neumann[34] and others have observed instances of low red blood cell counts and percentages of hemoglobin which improved. Osler[35] asserted that an anemia is not an essential feature of the disease. Many observers have recorded the fact that usually there is an increase in the lymphocytes. This is in accordance with the status thymolymphaticus. Brown,[36] of the Mayo Clinic, in a study of 17 cases, found anemia in 6 per cent. In 3 of 5 cases the cell volume index was increased. Normal circulating blood and plasma volumes were found in all but one case. In one instance, during an acute suprarenal insufficiency, a decreased percentage of water, of blood, and of plasma were noted. An anemia, he concluded, when associated with Addison's disease is not the result of a dilution, or an increase in total blood volume since large blood volumes did not exist in the presence of anemia.

Recently, A. L. Brown[49] has called attention to retinal pigmentation in an instance of Addison's disease.

Not many blood sugar determinations have been reported on these cases. Porges[37] thought from animal experimentation and from clinical studies that a reduction in the amount of blood sugar was a constant finding after suspension of the suprarenal function. Rosenow and Jugutts[38] subjected the instances of low blood sugars as were reported in the literature to critical study and concluded that a low blood sugar was not a common finding. These observers found in the Addisonian patients that the blood sugar fluctuated around normal. They further stated that the difference between the blood sugars of the normal individual and that of the Addisonian patient was that after injection of epinephrin in the Addisonian

there was never a hypoglycemia. Chapman[39] has performed sugar tolerance tests and found the curve to be remarkably flat.

Rosenow[40] observed a lowered kidney function as evidenced by an impaired elimination of water and solids in Addisonian patients. This is exactly what would be expected physiologically, due to the lessened amount of blood passing through the kidney.

Högler[41] has presented evidence that there is a hypoepinephrinemia by using Dietter's method of determination of epinephrin.

Loeper, Decourt and Ollivier[42] have recently reported experimental studies, as well as clinical observations, that in suprarenal melanoderma the melanin is an aminosulphurous substance. The suprarenals normally, in some way, influence the elimination of sulphur—therefore obliteration of suprarenal function increased the amount of sulphur in the organism. The high sulphur content of the blood with the melanoderma suggests that it may be a factor in the pathogenesis of the pigmentation. Bittorf[43] thought the bronzing of the skin was due to an increased amount of oxidase in the skin.

Prognosis and Treatment. Prognosis and treatment are equally discouraging. Neither Addison nor Trousseau ever observed an instance of recovery. The cases recorded as recoveries, according to Ferrando and Saloz,[44] are doubtful. The cases, such as the one reported by Tieken,[45] are instances of suprarenalopathies and have no right to be diagnosed Addison's disease. If the instances of suprarenalopathies are diagnosed Addison's disease then the syndromes described by Loeper, Carles and Jousé should be diagnosed as such. It is no more correct to diagnose a patient's condition as Addison's disease, if the symptoms appear during the course of an active infection in the lungs or elsewhere, than it is to make a diagnosis of nephritis, because blood is found in the urine during the course of bacterial endocarditis. The course of Addison's disease is usually unaffected by complication with other diseases. It has been thought that the advent of pregnancy is a very serious complication. Fitz-Patrick[46] has recently surveyed the literature and found 11 such cases reported. He reported a case and concluded that pregnancy, labor or the puerperium has little influence except the pigmentation is exaggerated during pregnancy but clears up somewhat after delivery.

Little can be done in the way of treatment. Rowntree[47] claimed results after using the Muirhead régime. Ephedrin[48] has been used but is inferior to the Muirhead régime. Many have been disappointed after suprarenal transplants.

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A STUDY OF BEHAVIOR IN THE NEWBORN.

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The object of this study has been to discover, through neuromuscular and other reactions of the newborn, whether one can tell anything about the psychology of the day-old baby. And if one can, then to determine whether these investigations can be made the basis for a prognosis in individual cases as to their mental equipment. In other words, it is an attempt to approximate investigation already made upon the mental make-up of children nearer to the time of birth than has been done. The practical application of such a method is obviously to ascertain at the earliest period of life the mental equipment and personality of the individual and its chance for normal development.

This paper is a record then of the reactions of 75 healthy babies to certain external stimuli during the first twenty-four hours of life, and the reactions of the same babies to the same stimuli during the second twenty-four hours of life. Tests were added as the need was shown, and some omitted on occasions. Two side studies have resulted. One is an examination of some of these same babies at three, four, six months and older to compare them with mental standards already published. These tests which are proving most interesting as a follow-up cannot here be presented. The second is an attempt to fix the best time from the infant's standpoint for

the first time of going to the breast; whether it should be in two hours, in six hours, or later, even to the next day. This too will be omitted from this paper.

The babies examined were from three sources in Washington, namely: From the white and colored wards of Columbia Lying-In Hospital, from the Crittenton Home and from the private practice of several obstetricians. One-fourth were colored and one-fourth were private cases. More than half were children of primiparæ and more than half (39) were boys.

The physical examinations made to establish their claims to normal physical conditions were such as could be made by the physician trained to the examination of the baby with the aid of the stethoscope and the tape measure only. In addition, the health of the babies was followed for ten days sufficiently to know that no one of them developed a disease of the newborn which might affect the reactions.

The measurements in themselves present some interesting features. Two of them are here mentioned: First, the wrists and ankles were rather diagnostic. If there was much loss of weight in the twenty-four hours between measurements the wrists and ankles or both invariably measured $\frac{1}{8}$ to $\frac{1}{4}$ inch less in circumference the second day. This should call for special attention by the physician. The second and most interesting measurement was that of arms and legs and their relation to each other. The arm was measured from the recess above the greater tuberosity to the tip of the middle finger, holding the arm straight. The leg was measured from the recess above the greater trochanter to the lower edge of the heel, holding leg straight and foot at right angles to leg. In the early cases it was noticed that the measurements for arm and leg were usually the same. Upon correlating the measurements with the history it was found that if the arm were longer than the leg (Cases 26, 39, 47, 65, 68, 69) that baby was born before term, and if the legs were longer (Cases 34, 45, 64) the baby had arrived four days to two weeks after the date expected. In 2 cases there was disagreement, but this measurement seems to be an accurate guide to maturity.

As health was essential for further study, it may be understood that all findings in the physical examination were normal. Knee kicks were active in every case and Kernig's sign was present also. In this series of 75 babies, 73 have a record of Babinski's sign.[1] Five were negative; 68 were positive; 28 of the 68 gave both negative and positive signs. The toe usually curled down first and then with persistent stimulation gave the Babinski sign. This plus and minus Babinski was so common that it suggests that some of the myelin in the pyramidal tracts was developed in the baby.

Various spontaneous activities may be observed during the first few hours after birth; crying, fixation (light), yawning, sneezing,

thumb sucking, hiccoughing, kicking, sighing, mouthing, coughing, sucking, stretching, grasping, urination, defecation, vomiting, erection, nystagmus, salivation and lacrimation. All of these have been observed in more than 1 and usually several of these 75 babies. In addition, 1 baby (Case 39) was observed by doctor and nurse on her first day to move the muscles of the cheek and mouth into that position which we speak of as a smile. She was incidentally about ten days premature.

Before taking up certain tests that were applied, it may be stated that no tests were made that could in any way be criticized as offensive. Every physician knows that the newborn baby must cry for its own physical well-being (to expand the lung tissues) and is made to do so by slapping or pinching. He also knows that the baby's lungs are not fully expanded after the first cry and that successive cries over a period of days or weeks are of advantage to the expansion of lung tissue. Slight pinching of the foot became an important part of the routine the first and second days, and was tested on the 75 babies. The response so almost uniformly obtained was surprising because the day-old baby has not been given credit for learning anything. On the first day when the foot is pinched the baby cries and waves his legs around in the air aimlessly. On the second day when pinched the foot is quickly drawn away and the cry follows. That order was practically always maintained: First day, cry, no drawing away; second day, drawing away, followed by a cry. Sometimes the second trial was made later in the first day, but the response was usually of the lesson learned, namely, drawing back and crying. Ten babies drew back on the first day (Cases 41, 42, 45, 47, 59, 60, 63, 65, 74, 75), 9 white and 1 colored. Only 2 babies failed to draw away the second day (Cases 46 and 57), 1 white and 1 colored. One test was that of pinching the inside of the knee to see if the other foot would come up and brush that knee. Tests were made on 26 babies; 20 responded with a cry and the usual waving of the legs; 6 brought the other foot up to brush the spot pinched. These 6 were all white, 3 males and 3 females. Three were private cases and 3 were Crittenton Home cases. Only 2 reacted both days. Pressing the hand against the soles of the feet to see if they would resist by thrusting back in 33 cases, yielded no response in 24, but in 9 instances the child thrust back against the hand. Three of the 9 were also 3 of the 6 that brushed the knee in the preceding experiment. Of the 9, 1 was colored and 8 were white; 6 were females and 3 were males.

Striking differences in reaction of 2 babies examined the same day are sometimes observed. Case 57 when his foot was pinched gave only a delayed cry the first day and failed to draw up on the second day. He did not brush his knee when pinched nor did he show an extensor thrust. Case 59 drew the foot away the first day as well as the second when pinched, brushed when his knee was

pinched and pushed against the hand. The resistance on the one hand and acquiescence on the other indicate differences in mental process and personality reaction. In this study of day-old babies one gets impressions not only of personality but also of "brightness" or "dullness." These impressions at first partly suggestive, and therefore unreliable, can now be gauged by objective reactions to certain tests.

During this study two phenomena have come to my attention. One is the walking phenomenon, to which attention was called by a nurse. A day-old baby, if held under the arms and lowered so that the toes touch the table, pushed on it with a walking motion. The second is the "crawling phenomenon of the newborn," described by Bauer.[2] A baby, if placed on the abdomen and pressure is made upon the soles of the feet, moves forward, the arms taking part. He says it is present at birth and up to four months.

Special Senses. *Touch.* No special test was made for this sense. Infants could easily be aroused by a light touch on the arm even when a sharp sound failed.

Taste. A few grains of salt were placed inside the lower lip. The reaction in practically every case was apparently pleasurable with some or all of the following reactions: Mouthing, smacking lips (heard 4 feet or more away), running tongue out and frequent salivation.

Smell. Babies have a very keen sense of smell. I recall 1 baby when taken to the breast for the first time reached out and opened his mouth when within 2 inches of the mother in spite of the fact that his eyes were tight closed and he had not touched her. The babies were tested with mother's milk on an absorbent cotton pledget held near the nose. When asleep there was no reaction. When nursing time was approaching, although lying with eyes closed, each baby's nostrils dilated and each mouthed. About 15 babies were tested with aromatic spirits of ammonia, placing it near the nostrils. If asleep they jumped and drew the head back, cried or blinked, dilated nostrils and usually mouthed. If awake they turned the head away, cried momentarily and usually mouthed. One-third of them sneezed and one-half brushed the hand scross the face. Usually the right hand was used; in 1 case it was done with the left hand.

Hearing. There are those who maintain that a baby does not hear at birth.[3] On the other hand, many a home requires quiet because the baby is asleep. I believe that the first is not true and that the second is unnecessary. Fifty-five babies in this series were tested for hearing. A snapping beetle was used; slapping the hands together had been tried but was unsatisfactory because of possible air currents causing a reaction. (Whenever possible they were tested not only while awake but when asleep.) When asleep the snapping of the beetle within 1 inch of the ear failed to stir all babies

except 2. The babies responded to the snapper according to their various conditions whether just awake, wide awake or crying. Of 29 babies tested while crying, 27 stopped crying at the sound. Twenty-six responded to tests when awake and not crying. Quite a few of these blinked, some flinched at the sound, some quivered, some opened the eyes and rolled them around and two turned toward the sound (Cases 18 and 68). Six babies gave no response to the hearing test. To sum up, babies generally show unquestionable evidence of hearing; but they sleep through noises if not jarred at the same time.

Sight. Sight is probably the most difficult special sense to test. There are two reasons for this—the medication of the eyes at birth and the fact that the baby tends to sleep most of the first two days. It is a matter of common observation that many babies when first born before being removed from the mother's table turn and appear to focus the eyes on a bright light, even when the light is sufficiently far away that the warmth does not reach them. Certain examinations were made as follows: Every baby tested for the pupillary reflex reacted to light at once. All eyes moved: (1) In a rotary motion; (2) up and down; (3) back-and-forth. The movements were practically always binocular. It was exceptional when the baby was well awake to have the eyes move separately or at different rates. Irregular movements were very common, especially in a right and left motion, when the baby was drowsy. Several showed temporary nystagmus and sometimes strabismus. Case 16 developed internal strabismus between the first and second examinations. On the first day the eyes appeared definitely normal, whereas the second day showed an internal strabismus which is still present at eighteen months. Delivery was by the breech and a rubber tube had been passed to the mouth. Many contusions were found on the second day. This baby was not tested as to sight.

Evidence of focusing was more difficult to obtain, but was definitely demonstrated in 23 of the babies. One baby (Case 26), born three weeks ahead of time, definitely focused down on a nearby object. Occasionally a baby (Cases 29, 69, 73) focused so close that internal strabismus appeared during the act. Another baby (Case 41) looked around, turned her head toward the nurse, then moved her eyes and fixed them for a few moments on the nurse's face. A sheet of white paper brought quietly but unintentionally within range caused another baby to move the eyes and fix the object and follow it as it moved away. The most convincing incidence of actual vision was Case 8, aged twenty-eight hours, who was crying hard in an otherwise quiet nursery. As I came into view the baby moved her eyes, focused on my face and stopped crying at once. As I moved forward the eyes followed, focusing on my face above the crib. After a pause I moved on and when well out of sight, the baby began crying again and continued vigorously.

Summary. Conclusions that may be drawn about the normal healthy day-old baby are:

1. Most of the special senses are used immediately after birth; all may be.

2. The day-old baby has many activities.

3. Babies at birth have individuality and personality, as shown by their varied performance.

4. Babies learn the first day of life; so that formation of habits and character begins then.

5. Finally, it may be said that studies of the reactions even at this early age may be of value in estimating the mental capacity of the baby, and that it may be possible to derive sufficient information even from a newborn infant to make a fairly reliable prognosis of the future development.

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ADENOMA OF THE SALIVARY GLANDS.

With a Report of a Possible Case.

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Among 151 tumors of the parotid region studied in the preparation of a recent contribution,[26] there was 1 in which the histologic structure differed so greatly from the others as to suggest that it belonged to an entirely different genus and to excite curiosity, the gratification of which, after a somewhat lengthy research, resulted in the collection of data upon which the present considerations are based. The tumor is mentioned at the end of the general tabulation in the earlier paper,[26] where it was classified as an adenoma. The details regarding it are as follows:

Case Report.—Mr. J. B., a decidedly slender white man, aged seventy-one years, a druggist by occupation, whose family and personal histories seemed devoid of interest with respect to the local disturbance that brought him under observation, began treatment at the Philadelphia General Hospital, January 18, 1923, for a tumor, the size of a hen's egg, situated on the right side of the face, just below and anterior to the ear. The

lesion had first been remarked about three years before, as a little "lump" and had grown steadily to its present size. There had been no known traumatic or other disturbance to explain its presence, at no time had it caused any pain and it was neither red, nor more sensitive than the surrounding structures. It was without fluctuation, firm, freely movable beneath the skin and in its bed, and unattached to the bone.

A radium application made that day caused it to swell to about four times its volume and to become tender. The patient was admitted to the wards on January 23rd, and on January 25th Dr. J. B. Carnett operatively removed it under gas anesthesia. An uneventful recovery followed, and the patient was discharged on January 27, 1923.

The patient, who lives in another city, in the last letter received from him, March 1, 1927, stated that the scar is "scarcely noticeable," that at the position formerly occupied by the tumor there is a "very slight hollow" and that the salivary secretion is the "same on both sides; no dryness."

The general appearance of the tumor is shown in Fig. 1. It measured 4.5 by 4 by 2 cm., was dark brownish-red in color and soft in consistency. It was solid, not cystic and one small part of its substance was darker, softer and more friable than the rest, and seemed to be made up of "glandular tissue."

Concerning its histological structure the hospital pathologist wrote the following: "The tissue showed what appeared to be normal parotid gland, with the exception of a small piece, which showed chronic inflammation. If the gland be enlarged grossly the diagnosis of *adenoma* would probably be justified."

When this material was reviewed certain corrections and additions seemed desirable, for the tissue did not appear like "normal" parotid gland, and there is some doubt whether the tumor is an adenoma.

The parotid gland is a serous gland, with secreting tissues all of one kind as contrasted with the submaxillary, which is both serous and mucous. It is divided into lobules, separated by partitions of connective tissue, in which the bloodvessels and larger ducts are supported. Each lobule is made up of a great number of short, curved tubules, closely packed together and separated by a few connective-tissue fibers, capillary bloodvessels and occasional elongated nuclei belonging to cells of uncertain classification. Each acinus or glandular tubule is composed of large pyramidal epithelial cells, arranged with their bases directed outward, and their apices inward, so as to form an irregularly spherical or spheroidal mass, the component cells of which are in contact by broad flattened surfaces. Very rarely can a lumen or opening be seen in the center. The nuclei of the cells are nearly always much closer to the bases of the cells than their apices, so that they seem to accentuate the peripheral border. A supporting basement membrane is commonly described, but it is rather of theoretical than of real occurrence, and even in tissues especially stained to demonstrate it, may be missing. Among the glandular acini are the intralobular ducts. In animals they are numerous and striking objects, each surrounded by a sheath of fibrous connective tissue, much as in the human pancreas;

but in human parotids there are no such investitures, and the ducts do not differ in any other manner from the acini than by a wide-open lumen and in the quality, difference and appearance of the epithelium lining them, which is smaller, cuboidal and with distinctly eosinophilic cytoplasm.

This is, for the most part, well shown in Fig. 4.

When the hospital pathologist, not having for a long time seen a section of normal parotid gland, first glanced at the sections of this tumor he saw what is shown in Fig. 2, received the general impression of glandular tissue and, knowing that it came from the parotid gland, thought that he was seeing "normal parotid gland tissue." But under a higher power that impression should have been corrected.

In the sections of this tumor the absence of ducts is striking, the only one found being that shown in Fig. 3. It is possible that other ducts may have originally been there, but it is doubtful, and if so, they have been obscured by changes incidental to the radium exposure. But that does not matter; they are not now visible or recognizable, so that the supposed resemblance to "normal parotid gland" does not exist.

Passing next to the glandular or acinar tissue itself, the resemblance to parotid gland structure is really very slight, as is shown by reference to Figs. 5 and 6. There are no acini, though there are groups of cells that by a stretch of the imagination may be supposed to correspond with them, and may, in fact, once have been them; but, if so, are now so altered by the radium as to be extremely doubtful.

The lobules with the strikingly glandular appearance under the low power are found, upon more careful examination with higher powers, to be made up of small collections of cells with no definite arrangement at all.

Not a single definite acinus could be found in an entire section measuring 1.5 by 1 cm. There were multitudes of small cell aggregations or clusters, but no definite secretory arrangement of any kind. There were no cells of pyramidal shape; the cells were, for the most part, almost spherical, with centrally situated nuclei.

It is unfortunate for our purposes that the tumor was ever treated with radium, for it is undoubtedly a very unusual one, and it is a pity not to be in a position to know how it originally looked, and not to be more definitely able to determine what it really was. It certainly was chiefly composed of what resembles glandular epithelium, arranged in lobules, composed of groups of cells that may once have been acini, but now are no more clearly so than those of some carcinomas. Here it should be stated that the supposed effect of the radium did not show itself in the death of the cells, but in their swelling, detachment and separation, by which any glandular arrangement ever existing must have been destroyed.

Any preconviction was sufficient to confuse the examiner: Thus, a section was shown to a friend, with the casual remark that it was an interesting case of hepatic disease, and, being forbidden to move the slide, he acquiesced, and believed that he saw hepatic cells. To another a different part of the same section was shown as a diseased adrenal, and accepted as such. These experiments were not merely facetious, but were serious and intended to prove that the structure was so fundamentally altered as not any longer to be recognized by one unacquainted with the source of the material. When the very hospital pathologist by whom the original diagnosis of "adenoma" was made was shown a section of normal parotid gland and one of the tumor side by side, he could no longer find the evidences upon which he had at first based his diagnosis, and admitted that the differences were great.

The tumor probably merits the name adenoma as much as most of the tumors of the salivary glands that have been so described, but final opinion as to whether the name is justified or not would better be reserved until the reader has perused what is to follow.

If the tumor just described be an adenoma then I found but 1 among my series of 151 salivary gland tumors, that is, 0.662 per cent. But if one looks for adenomas of the salivary glands in the literature he may find 30 among 269 tumors, referred to under some variation of that name—adenoid tumor, fibroadenoma, adenofibroma, adenolymphoma, lipoadenoma, adenoepithelioma, cyst-adenoid tumor, cyst adenoma, cystic adenoma, papillary cystadenoma, while 14 (5.2 per cent) are called adenoma without any qualification. It would, therefore, seem either that adenoma of the salivary glands is ten times more frequent in occurrence in Europe than in America (there is only a single American reference to adenoma of the salivary glands), or that there is a far greater latitude in the employment of the name on the other side of the Atlantic Ocean. The latter explanation seems the more probable, but in order to be sure it is necessary to investigate, and to find out exactly what different authors mean when they speak of adenomas.

Gould's *Medical Dictionary*, which has probably derived its definition from the best writings, and framed it to express all of the various usages, defines as follows: "An adenoma is: (1) An epithelial tumor constructed after the type of a secreting gland; (2) any tumor which has as its characteristic feature tubes or spaces lined with epithelium, whether or not it arises from or is connected with a gland."

The definition is, however, imperfect, for there are numerous and dissimilar glands, some of which, the adrenal and the liver, for instance, that have no "tubes or spaces lined with epithelium."

Adenomas are supposed either to arise from a rudiment of the same cellular material as that from which the gland proper arises, or directly from the gland itself, hence every adenoma more closely

resembles the gland in relation with which it grows than any other. Thus, in the so-called adenomas of the kidney the structure is tubular; in those of the adrenal and liver, columnar; while in the salivary glands it should be racemose. In most cases some question as to the actual source of the tumor tissue may be asked. Are the tubules of the renal adenomas truly renal tissue, or do they consist of some other accidentally included in it—vestiges of the Wolffian tubules, adrenal cortex and so forth? Are not some adenomas of the liver but rearrangements of liver tissue, recovered and regenerated after destructive disease and not morbid growths, as ordinarily understood?

It must also be remembered that some adenomas vary in appearance according to physiologic and other conditions. An adenofibroma of the breast in a virgin differs greatly from one in the breast of a lactating woman. In either case the tissue of the tumor may differ so widely from that of the breast itself as scarcely to resemble it at all—intracanallicular adenofibroma.

To some, especially surgeons, the term adenoma seems sometimes to be but a convenient means of signifying that a tumor is supposed to be innocent and not malignant. Such purely clinical usage is unfortunate.

In general, the benign epithelial glandular tumors present a regular or "typical" histologic structure; the malignant ones, a confused, irregular or "atypical" structure. Such typical, regular and orderly arrangement has been made the basis of classification by many, but in the alimentary canal occasional tumors are encountered whose growth is characterized by invasion and destruction in spite of the histologic orderliness of their structure. To provide for them, the term "destructive adenoma" was introduced, and later abandoned, all such tumors having proved in the end to be but early stages of carcinoma.

Adenomas are usually—perhaps always—surrounded by a "capsule," or fibrillar connective tissue layer, by which they are completely separated from the gland in relation with which they occur. Each is, therefore, a distinct and separate entity, and not a part of the gland. Should it be shown to be connected with the duct system of the gland, it would be a part of the gland—a hypertrophy of a lobule—and not a true morbid growth. Bloodgood in his writings has caused confusion by the employment of the phrase "uncircumscribed adenoma" when there is no distinct morbid growth, but only a localized irritative enlargement of glandular lobules. In examining sections showing the condition one finds that the nearer to the important lesion—a cyst, for example—he examines, the larger the lobules are, and the farther from it, the smaller they are.

No enlargement of an entire gland should be regarded as an adenoma. It is a hypertrophy, and not a tumor—unless it can be

shown that a growing tumor has actually destroyed and replaced the organ.

When it is remembered that French authors call all malignant tumors "cancers," and therefore find it necessary to differentiate between "epithelial cancers" and "connective tissue cancers," one need not be surprised at any latitude in the employment of terms on their part, and it has been, indeed, they that have employed the term adenoma most broadly.

In the existing uncertainty as to what any tumor is, and from what it grows, it may not be possible to be either accurate or consistent in the employment of terms, but the more carefully every term is employed, the more certain will it become that those using it will mean the same thing.

The present paper deals with adenoma as it occurs in the salivary glands, but nowhere is it more important to be careful in the use of the name, because of the rather frequent occurrence in those glands of the mixed tumors with which others may so easily be confused.

In spite of opinions to the contrary, the most satisfactory theory by which to account for the occurrence of the mixed tumors seems to be that of Cuneo and Veau, that supposes them to grow from residual embryonal vestiges of structures not used up during the complex development of the regions in which they occur. Supposing that to be the case, such vestiges, sequestered and temporarily suppressed, may contain cells of the ectoderm that covers the face and lines the mouth, mesodermal elements belonging to those that form the cartilages of Meckel and Reichert, and antecedents of the glandular epithelium from which the salivary glands themselves grow, as well as occasional vestiges of voluntary muscle, lymphoid and adipose tissues.

Not all of these tissues are to be expected in any single tumor, but in a long series all may be found, singly or in various combinations.

Cartilage is perhaps the most frequent and most striking tissue of the mixed tumors, and not a few pathologists refuse to consider any tumor of the salivary glands a mixed tumor unless it be present. But it is frequently lacking, its place being occupied by a soft mucoid tissue sometime supposed to be its antecedent, giving the tumor much the same appearance, though, as it has neither the same density nor the same staining reactions, such tumors are soft.

In reality the cartilage and mucoid tissues are neither so frequent or so characteristic as a peculiar cellular tissue that has long attracted attention because of the uncertainty of its origin and destiny. It consists of short cells, usually described as of spindle shape, though, as a matter of fact, more of a lozenge shape, forming strands and sheets, twisting and curling about or penetrating into the more dense elements, sometimes in relatively small quantity,

sometimes in such abundance as to constitute the chief component and to cause the tumors to be mistaken for sarcomas of the spindle-cell type.

These cells were responsible for Volkmann's opinion that the tumors arose from the endothelium, and led to the belief that they underwent malignant—"sarcomatous"—degeneration, and have puzzled most of the pathologists that have studied the tumors. Fraser, who follows the older French school, and believes that the mixed tumors are derived from the glandular tissue of the salivary glands themselves, conceives these cells to result from the multiplication of the "basket" cells, or outer layer of the glandular tissue.

Bosc and Jeanbrau may have given a better explanation, at least one definitely in accord with the theory of origin from sequestered embryonal tissue, and regard them as "indifferent" epithelial cells, that is, cells too immature to have yet manifested their inherent tendencies, and therefore probably capable of developing along different lines. If, in one after another of a series of mixed tumors of the parotid, one examines these cells it may be possible to recognize the following apparent diverse evolutions: From spindles one passes to short lozenge-shaped cells with straight parallel sides, separated by uniform but narrow intervals, across which occasional delicate protoplasmic bridges may be found to pass from cell to cell, becoming more and more numerous as a certain direction is followed in the examination of the tissue, until definite acanthous epithelial cells, among which small but distinct epithelial pearls may be found, is reached. An occasional tumor developing along this line eventually may present an appearance much like spinocellular carcinoma.

Followed in some other direction, the "indifferent cells" lead into collections of glandlike units, rare in some tumors, many in others and in still others constituting the greater part of the structure. According to the regularity or irregularity and relative quantity of such glandular tissue, the respective tumors may be looked upon as adenomas or carcinomas respectively.

In most of the tumors enough admixture of the customarily present cartilage and so forth will be found to enable the diagnosis of mixed tumor to be made, and it is because of their almost invariable presence in some part of the tumor that the occurrence of adenoma in the salivary glands is doubted by many careful pathologists. It was because of these diverse appearances that mixed tumors were thought to undergo both sarcomatous and carcinomatous degeneration until, in the paper above quoted, it was shown that nothing in the histologic structure or appearance of the mixed tumors gives indication of their future course or how they will behave clinically. Tumors that seemed to be histologically typical of sarcoma and carcinoma never recurred after removal; others

devoid of histologically malignant appearance recurred again and again and killed the patient, though by local growth and invasion only, and without metastasis to the lymph nodes or viscera.

To be an adenoma the whole tumor should show typical glandular arrangement. How do the published cases of adenoma of the salivary glands meet this requirement? It will be well to begin by an examination of the only reported American case, that of Schutz. It lends itself most kindly to investigation because it not only contains verbal descriptions of what the writer is talking about, but is illustrated with photomicrographs that make it impossible to misunderstand him. This is what he says: "The definitely spindle-shaped cells tend to run in parallel lines, but as they take on a polygonal or oval shape there is a tendency for them to be arranged in whorls. Many of these whorls are composed of solid masses of cells arranged in circular fashion, but some contain spaces in their centers, forming thereby structures strongly suggestive of young acini. This impression is substantiated by the fact that in each lobule there are numerous examples of definite acini composed of cuboidal typical glandular cells surrounded by a membrana propria and containing, as shown by appropriate staining, mucus in their lumina."

From this description it is evident that the author thought of the tumor not really as an adenoma, but as "becoming" one.

But neither what he says nor what he figures in the illustration is adenoma. In each case it is typical of a mixed tumor. His Fig. 2 might have been photographed from almost any one of 36 of the mixed tumors of the series used in the preparation of the previous paper. If such an inconspicuous number of glandular elements were sufficient to cause a tumor to be classified as such, adenoma would be one of the most frequent instead of the most rare and debatable of the salivary gland tumors.

When other reported cases are carefully considered many of them, like Schutz's case, seemed to be only mixed tumors of the usual type.

In 1869 Ancelet[2] removed a tumor from the parotid region of a woman, aged sixty-five years. Lancereaux examined it and called it an "adenoma," but Broca, who also examined it, reserved a diagnosis. In one year the tumor recurred, and seven months later the patient died. That clinical course is not in keeping with the diagnosis of adenoma.

In 1877 Jalaguier[18] reported a "fibroadenoma" of eight years' duration, and the size of a walnut, that he removed from the parotid gland of a girl, aged eighteen years. It contained no cartilage, but what is said about it would apply to any mixed tumor, and there is no evidence that it was unusual.

In 1879 Dunlop[8] reported a tumor of two years' duration removed from a woman, aged thirty-six years. It was situated in front of

and below the right ear, where it appeared two years after a traumatic injury. It was removed with the thermocautery, and when cut open appeared "exactly like the roe of a cod." Under the microscope "the section exhibits closely packed, rounded and oval masses, separated by a thin stroma, and under the high-power these masses seem to be composed of gland cells arranged around the wall of the acini as well as completely filling up their interiors."

In 1892 Cale[6] reported an "adenoma" of the left parotid gland, of three and a half years' duration, the size of an orange, in a woman, aged forty-one years. As the report does not deal with the pathology of the tumor, and contains no description of its microscopy, there is no certainty as to what it really was.

In 1897 DeMarco[7] removed an "adenoma" of nine years' duration, and the size of a mandarin orange, from a woman, aged thirty-seven years, but the diagnosis was made clinically and confirmed by gross examination only.

In 1910 Stuart-Low[39] reported a case of "cystic adenoma" of the facial parotid gland, that had existed for "many years" in a woman, aged twenty-four years. The microscopic description is such as to exclude it from, rather than to admit to, the group of adenomas.

In 1919 Laignel-Lavastine[21] reported a "fibroadenoma" of the parotid the size of an egg, that was removed from a man, aged forty years. The description is very brief, and gives no justification for calling it an adenoma.

From the "adenomas" it is but a short step to variations such as these:

In 1886 Cabadé[5] published "Observation of a Cystoadenoid Tumor of the Parotid." It had existed for three years in the right side of the face of a man, aged fifty-eight years, and attained to the size of a walnut. Nearly all of the contribution is clinical, but enough is said to suggest that the growth was a mixed tumor.

In 1896 Mermet[25] removed what he described as "tubular cystic adenoepithelioma," the size of a pigeon's egg, from the left parotid of a white woman, who had observed it for six years. When it was examined microscopically the largest cyst was found to be lined with several layers of columnar epithelium and partly filled with vegetations. It was not thought to be a mixed tumor "in the ordinary sense;" it was no more an adenoma.

In 1908 Terrier[41] removed a tumor of seven years' duration, the size of a walnut, from the right parotid of a white man, aged twenty-eight years. Upon microscopic section, it was found to contain small cysts with vegetations covered with cuboidal or tall epithelium. This case has been frequently quoted as an adenoma, but without sufficient justification.

In 1911 Lambret and Pelissier[22] studied a small tumor that had existed for two years in the left parotid of a white girl, aged seven-

teen years. From its microscopic appearance they considered it analogous to the intracystic papillomas of the breast. However, they used it as the starting point of their publication, "Adenomas of the Parotid."

In 1922 Ehrlicher[10] described a "papillary cystadenoma of the parotid region with a lymphoid matrix," but it has not been possible to obtain the journal in which it made its appearance.

In 1924–1925 Rikl[32] removed a plum-sized tumor of two years' duration from the angle of the jaw of a white man, aged forty-seven years. It was full of cavities into which excrescences grew. He called it "parotid papilloma," and found about a dozen references to similar cases in the literature.

In 1900 Bouglé[4] reported a "cystic adenoma of the submaxillary gland." It was of six to seven years' duration, of egg size, and occurred in the right suprahyoidean region of a white lad, aged sixteen years. The tumor was encapsulated, and on section was found to be lobulated, and impregnated with a colloid-like viscid liquid, making it look like a goiter. Milian examined it microscopically and found that the gland preserved its structure in many places, but that the lobules were separated by thickened connective tissue partitions.

Most of the lobules were greatly modified, the epithelium flattened until it became unrecognizable, and some of the acini were so dilated that they had fused. The lobules adjacent to ducts had their epithelium flattened and the lumen dilated. In many cases it was scarcely possible to distinguish the elongated epithelial cells embedded between the blocks of colloid substance.

This seems more like obstruction of a duct system than a tumor, and it is difficult to imagine why it was thought to be an adenoma.

In 1904 von Saar[34] observed a child, aged eighteen months, that had been born with a swelling of the right side of the face. It enlarged rapidly. The child died of measles, and at the autopsy it was found to have a tumor so large as to displace the larynx and trachea to the left. It was examined microscopically and described as a "cystadenoma." In discussing this tumor, Küttner says that it contained cartilage, striated muscle and lymphoid tissues.

In 1911 Vincent[44] described as a "cystic adenoma of the parotid" a tumor that had been present for twenty-four years, in the left parotid of a white woman, aged seventy-four years. During the last four years it had grown more rapidly than before, and reached the length of 10 cm. It was cystic, and when punctured permitted escape of serosanguinolent fluid. Upon removal it was found to be a soft tumor with secondary cyst formation, and the description is such as to make it more than probable that it was a mixed tumor.

The consideration of these cystic tumors naturally leads one to inquire how many and what kinds of cysts occur in the salivary

glands. They are far from common, or, at least, few are recorded in the literature, for Pietri,[30] who observed 1 in 1911, reviewed the subject and was able to collect only 10 cases. He came to the conclusion that they were all of congenital origin. A few other articles have since been published—one by Heath,[16] called "Congenital Cyst in the Parotid Gland," and one by Heines,[17] "Salivary Cyst." Heines thought his case to be a retention cyst, but considers its possible relation to lymphangioma, branchial and other cysts. It was multilocular, and when palpated before operation it felt like a "bundle of earth worms." It occurred at the age of seven years, and the little girl was only ten years of age when the operative removal was effected. Royster,[33] in 1922, reported another "cyst of the parotid gland" that occurred in a woman, aged forty-six years, being situated in front of the left ear, and extending downward on the neck. Unfortunately the microscopy of these recent cysts was not studied, so that their true nature is not known.

But there is reason to believe that instead of being retention cysts, as ordinarily understood, they are the final stages of congenital defects of development, not far removed from those more frequently expressed in the form of mixed tumors.

It is interesting to observe that a few of the reported adenomatous tumors were complicated by admixtures of most unusual tissues. Thus:

In 1893 Sacchi[35] observed "a most rare case of congenital acinar lipoadenoma of the parotid," in a male infant, aged six months. The child had been born with the tumor, that grew so rapidly that in four months it was as large as the head itself. Microscopic examination of the excised tumor showed it to be made up of adipose tissue through which glandular ducts and tubules ramified.

A tumor that may have resembled this was reported by Tansini,[40] as an "intraglandular lipoma of the parotid." The patient was a man, aged sixty-eight years, and the tumor grew in two years from the size of a pea to that of a pigeon's egg. It was soft and elastic, and under the microscope showed parotid tissue disseminated throughout an adipose matrix.

Very peculiar, and introducing another tissue into the matrices of the tumors, are a few characterized by the presence of lymphoid tissue. The first of these to be sufficiently described for classification is probably that of

Albrecht and Arzt[1] who found a papillary cyst adenoma, such as have been mentioned above, as occurring in the salivary glands, in what seemed to be a cervical lymph node.

Glass,[14] two years later, in 1912, reported a "branchiogenic papillary cystadenolymphoma of the parotid region" that appeared to be much the same thing in a slightly different situation.

Ehrlicher,[10] in 1922, observed another case, a "branchiogenic

papillary cystadenoma of the parotid region with a lymphatic tissue matrix."

These cases were carefully reviewed by Rikl,[32] who in 1924 and 1925, reported a similar tumor to which he gave the name "parotid papilloma." It occurred at the angle of the right jaw of a white man, aged forty-seven years. When microscopically examined it proved to be full of cavities, into which excrescences covered with columnar epithelium grew. The framework of the excrescences was largely composed of typical lymphoid tissue with germinal centers like those of lymph nodes.

Mazza and Cassinelli,[24] in 1923, also described a "rare papillary cystoadenolymphoma of the parotid region." It was about the size of a mandarin orange, soft, elastic and nonadherent, and was removed from the left parotid region. At the operation it was found to be subcapsular, and in contact with the gland. Sections showed a firm capsule surrounding a granular mass excavated by numerous cystic cavities, filled with colloid into which papilla projected. Microscopically the papillæ were composed of typical lymphoid tissue with germinal centers, and covered by a tall epithelium.

In 1923 Tortona[42] also published a paper entitled "Clinical Considerations upon a Case of Cystic Fibroadenoma of the Parotid," but it was impossible to obtain the journal and see what it really was.

In some cases the morbid growth of adenomatous appearance seems to be but part of the gland. Exactly what this intimate relation means, and whether it indicates some other lesion than a tumor, is uncertain. Here are some such cases:

Berger and Magrou,[3] in 1901, removed from the left side of the neck of a woman patient a tumor of ten years' duration and the size of a walnut. It was seemingly situated in the carotid region, at the upper level of the thyroid cartilage, and was easily removed under local anesthesia. Upon microscopic examination, it appeared to be a normal submaxillary gland, but a single lobe presented the appearance of a mixed tumor. They conjectured that it might have been a semidetached lobule of the gland, and, basing their thought upon that theory, advanced it as evidence that mixed tumors have their origin in the glandular epithelium.

Verneuil and Talazac,[43] in 1869, had studied a tumor of six years' duration, in the submaxillary region of a woman, aged fifty-eight years. It was gradual in growth, and had reached the size of a walnut. It consisted of two parts—one resembling the normal salivary gland, the other very different, and composed of fatty-appearing nodules.

On section, the knife opened a space the size of a small nut and a yellow mass escaped. The microscope showed well-developed glandular acini filled with cylindrical epithelium. The central part

was in a state of fatty degeneration. The vagueness of the description may, perhaps, be excused when the conditions of microscopic examination in 1869 are remembered.

Paquet,[29] in 1875, also described an "adenoma of a part of the parotid," but the journal in which it was published was not available.

But of the reported tumors, a few remain that seem more nearly to correspond with the preliminary requirements than those considered. Thus:

Duplay,[9] in 1875, removed an egg-sized tumor, of eleven years' duration, from the submaxillary region of a woman, aged forty-seven years. It was rounded, smooth, semi-fluctuant, mobile and easily enucleated, although attached by a firm pedicle the diameter of a goose quill.

Ranvier examined it microscopically, and says of it: "It is constituted of epithelial tubules, for the most part possessing dilated lumens." The epithelial cells "are striated like those of the ducts of the salivary glands." Between the tubules there was a firm tissue, most abundant at the periphery of the lobules.

Poncet and Chaintre,[31] in 1888, removed a peculiar submaxillary tumor of about eight years' duration, that, doubling its size in the last year, became as large as a mandarin orange. It was smooth, hard and divisible into two parts, superimposed and separated by a band. It was easily removed, and when incised partly emptied itself of a soft, white mass, recalling boiled rice in appearance.

Bard examined it microscopically and found it to be made up of epithelial elements of the salivary type, dense and well organized in regular tubules. The ducts were clear and distinct.

If his account had stopped there the diagnosis of adenoma might have been justified, but he adds, "It is probable that one is simply in the presence of vestiges of the gland," and so leaves the reader uncertain as to what the condition really was, especially as he further adds that there was "inflammation."

Wölfler,[45] in 1883, removed a fist-sized tumor from the submaxillary gland of a man, aged fifty years. It was adherent, and not all could be excised, so that it quickly recurred, necessitating a second, third and fourth operation, after which it became inoperable. It never metastasized to the lymph nodes or viscera. He described it, after microscopic examination, as "an exquisite adenoma." Its behavior was certainly like that of an ordinary recurrent mixed tumor.

All who study the tumors of the salivary glands, especially if interested in adenoma, cite the 4 cases reported by Nasse.

Nasse,[27] in 1892, personally studied and reported the following cases of adenomas of the parotid region:

I. This tumor occurred on the left side of the face and neck of a white woman, aged twenty-eight years, where it had grown slowly for eight or nine years, until the mass removed at operation

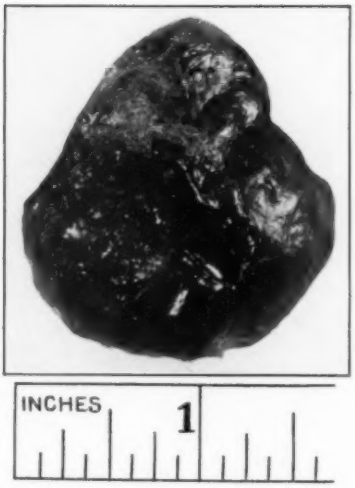

FIG. 1.—The entire tumor as it was received at the laboratory of the Philadelphia General Hospital, showing its smooth surface, lobulations, and the soft, rather dark interior exposed by an incision.

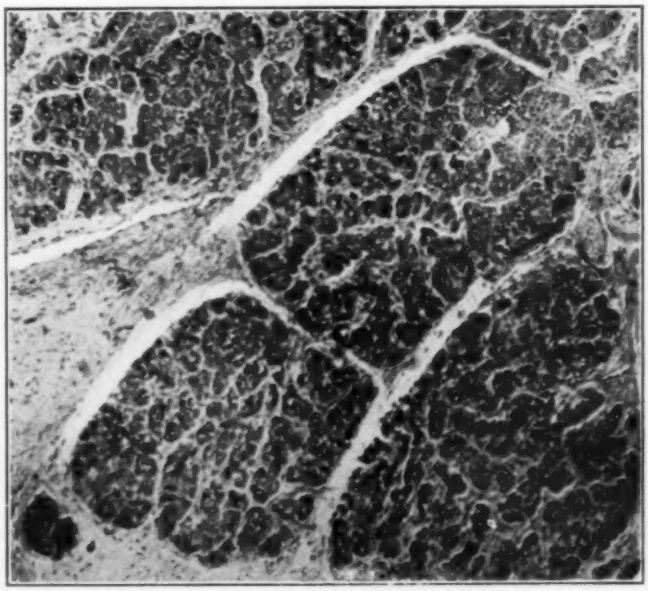

FIG. 2.—Shows a low-power view of a section showing the lobulations and the cells arranged in clusters easily mistaken, with this power, for acini of a regularly formed gland. It was this picture that caused the tumor to be called adenoma.

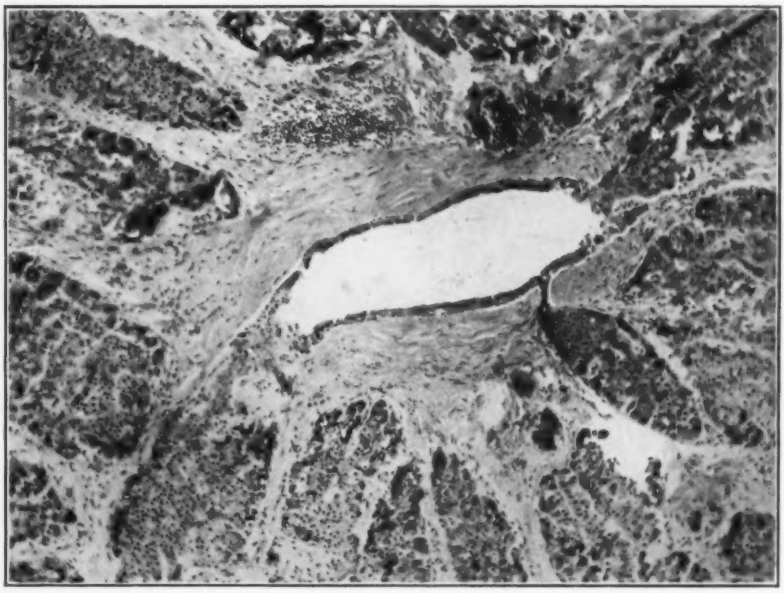

FIG. 3.—Low-power view of the only field in a large section, in which a duct could be found. The general structure appears glandular, acinous, and suggestive of a salivary gland, but the relation of the duct to the subordinate structure is peculiar and ambiguous.

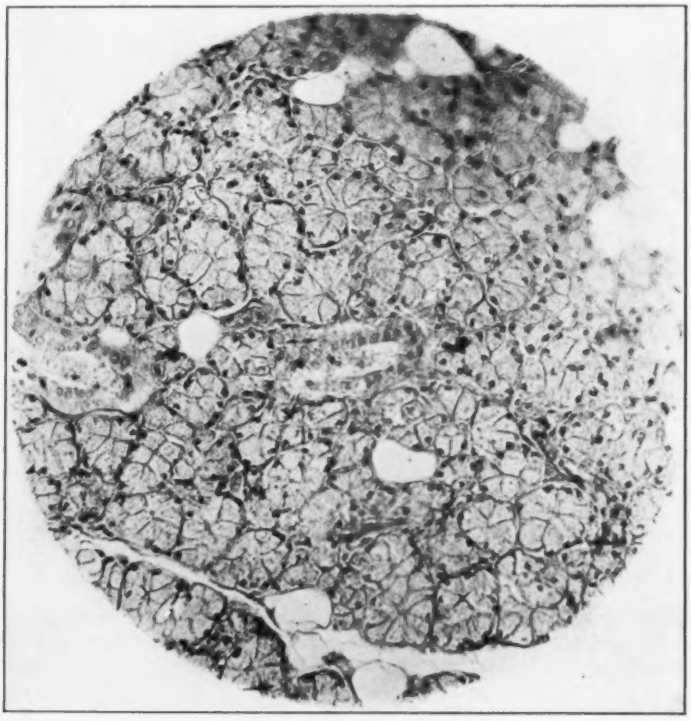

FIG. 4.—A section of a normal parotid gland from a young man executed by hanging. The acinous structure is beautifully shown with a sectioned duct in the center and another at the periphery.

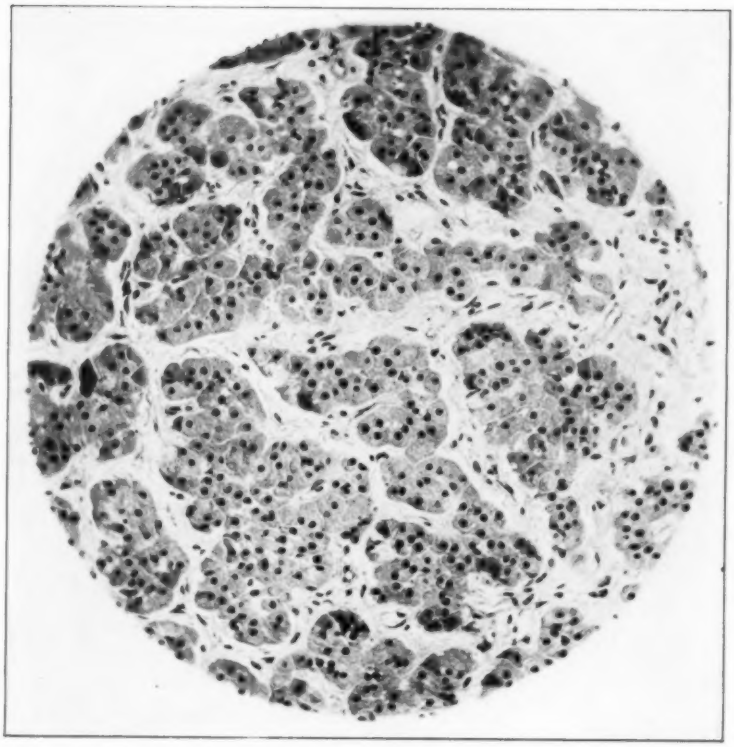

FIG. 5.—High-power magnification of a part of the field shown in Fig. 2 and on the same scale as Fig. 4. The resemblance to glandular structure and especially to salivary gland structure now largely disappears.

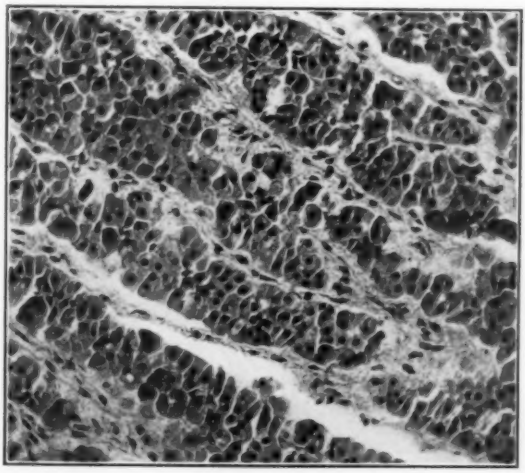

FIG. 6.—Another part of the same section, under the same magnification as Figs. 4 and 5, and with no resemblance to salivary gland structure whatever.

was the size of a large apple. It was soft, smooth, lobulated and encapsulated. Some parts felt spongy, and there were bean-sized hemorrhagic areas and softenings.

Microscopic examination showed glandular structure, all of the acini having lumens and being definitely separated from one another. Dilated acini were less regular in shape.

II. This tumor occurred upon the right side of the face of a man, aged fifty-two years, who had known of its presence for fifteen years. Recently it had grown rapidly, and it was as large as a goose egg. It was lobulated, firm, encapsulated and lay rather deeply in the parotid gland, the capsule of both being continuous, so that fragments of the gland were removed with the tumor. The cut surface was smooth and less granular than that of the gland itself. Microscopic examination showed definite glandular formation like that of the preceding tumor.

III. This tumor had existed for twelve years upon the face of a woman, aged forty-six years. During the last eighteen months it grew rapidly to the size of a hen's egg. At operation it was found to be soft, rounded, covered by the parotid, but separated from it by a thin capsule. Its substance was crumbly. Microscopic examination showed no definite separation of individual acini or lobules. There were epithelial cells like those of the normal parotid gland. The alveoli were small and crowded together in many places, and were not present everywhere. The lumens of the alveoli were partly filled with a slimy mass. There were also widely dilated acini lined by cuboidal epithelium resting upon a distinct membrana propria. There was no cartilage, no hyalin, no mucous tissue and no sarcoma-like tissue.

IV. This tumor, the size of a hen's egg, had existed for many years, upon the side of the face of a man, aged sixty-one years. At operation it was found to be attached to the parotid gland, though near the mastoid process of the temporal bone. It was well encapsulated, and consisted, in large part, of colliquation cysts filled with red-brown fluid containing blood pigment, cholesterin and cell débris. The solid part presented a definite lobulated structure, with brownish pigmentation. The cut surface was irregular, full of small cavities, porous and spotted with brown. Microscopically it was much like the preceding tumor. In many places the ducts and alveoli were dilated, the cells and stroma atrophic and some of the alveoli had coalesced, so as to assist in the formation of the cavernous and cystic spaces. There was much blood pigment.

Mixed tumors of the salivary glands are not of such frequent occurrence as to afford many pathologists an opportunity to study a large number and so to become familiar with all of the various appearances they present. It is not, therefore, surprising that when one of them deviates considerably from the commonly recognized type of structure, it is apt to be thought of, and perhaps

described as something rare or new. Each of the cases above reviewed was regarded in that way by its reporter, who named it according to its most striking individual features.

But if all of these cases are carefully considered with reference to one another they seem to form a series, at one end of which are the mixed tumors and at the other the adenomas. Between the extremes are intermediate forms filling all of the gaps and variously called papillary cyst adenomas, cyst adenomas, cystic tumors and fibroadenomas.

The newly reported case with which this contribution opens is probably as much like adenoma and as much like a salivary gland as any, but, as was pointed out, is really very little like either. The same seems to be true of all. Upon careful comparison with the gland itself, very little resemblance can be found, and one remains in doubt whether real adenoma of the salivary glands occurs. If so, it must be very rare, for there can be but little doubt that nearly all, if not, indeed, all, of the described adenomas are but mixed tumors of unusual appearance.

The cases of Berger and Magrou, Bouglé, and of Poncet and Chaintre, in which tumor and gland seemed to be blended in the new growth, have been seized upon by those believing the origin of the tumors to be from the glands themselves, as the result of injury followed by regenerative efforts, in turn succeeded by various miscarriages, interferences and metaplasias, in support of the theory. And when to these naturally occurring changes are added the artificial and experimental results produced in the salivary glands of dogs by Fraser,[12] the proponents of the gland-tissue-origin theory seem to have a pretty strong case. But on the other side are facts of great importance that must not be overlooked:

1. Fraser did not succeed in producing any tumors in the salivary glands of dogs. He only reproduced changes similar to those frequently found in tumors, where they may occur because of conditions resembling those experimentally induced by his ligations, obstructions, etc.

2. Of the 151 tumors studied in the preparation of the previous contribution, 1 was said to have occurred after a "severe twist of the neck," 3 after attacks of "sore throat," 3 were referred to diseased or extracted teeth and 1 was first observed "after typhoid fever." In 143 the tumors occurred without any explanation whatever, and in not a single one did the tumors begin with signs of acute inflammation. Others have mentioned traumatism as preceding the appearance of the tumor, but careful questioning failed to find it among the cases mentioned. Moreover, the larger moiety of the tumors occurred in women, who are much less subject to traumatism than men.

The almost invariable story told by the patients is that the tumor first made its appearance as a tiny nodule, developing for no

appreciable reason, and painlessly grew to a size exciting suspicion and apprehension of future trouble.

3. The development of the tumors is usually very slow. Several mixed tumors have been known to exist for more than half a century with very little change, which is unlike inflammation, and recognized histologic signs of inflammation are almost universally absent from their tissues.

4. This seems to be a cogent argument: Occasional mixed tumors, not to be differentiated from others occurring in the salivary glands themselves, are found in the neck, in no manner connected with the glands, yet having epithelial elements, so like the dilated ducts and acini of the salivary glands as to cause them to be called "adenomas." One of the malignant glandular tumors of our series had that origin.

Finally, if the tumors arise through changes in the gland structure, how can the occasional presence of striated muscle be explained?

Conclusions. 1. A new case of adenoma (?) of the parotid gland is reported.

2. Its histologic structure, at first seeming closely to resemble the parotid gland, is found upon more careful examination, to be quite dissimilar. In this regard it resembles all other reported adenomas of the salivary glands.

3. It does not aid in proving or disproving the contention that there are or are not adenomas of the salivary glands, for it seems to find its place at one end of a long series of tumors, at the other extreme of which are the ordinary mixed tumors.

4. The occurrence of gland-like tumors (adenomas) and of tumors containing varying quantities of glandular tissue, is no indication that such tumors arise from the glandular tissue proper, but simply goes to show that glandular tissue may sometimes preponderate over other tissue components of mixed tumors.

5. The origin of mixed tumors from the glands themselves seems to be inconsistent with some of the important facts known about such tumors.

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EFFECT OF PARATHYROID HORMONE ON BLOOD COAGULABILITY.*

With Special Reference to Jaundice.

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Surgery in the presence of jaundice carries with it the danger of serious postoperative bleeding, which may appear after even the most limited operative procedures, and lead to a fatal termination, despite all efforts of the surgeon to control it. Petren[1] has collected the statistics of the large Scandinavian clinics for the last two decades, and finds that cholemic bleeding has caused 10 to 15 per cent of all operative deaths in gall bladder cases, and that it has cost the lives of 1 to 2 per cent of all patients operated upon because of bile tract disease. Whatever other factors may play a part in this cholemic bleeding, certain it is that many of these patients, particularly those with long-standing, high-grade jaundice, have a greatly delayed blood coagulability and many procedures directed toward increasing the clotting power of the blood have been adopted in the effort to combat this tendency toward hemorrhage. Of the coagulants employed, calcium salts in one form or another have probably had the widest use. First advocated by Wright,[2] in 1891, calcium was for many years administered by mouth to patients in whom an increased blood coagulability was desirable. Schmerz and Wischo,[3] in 1917, found the intravenous injection of soluble calcium salts far more effective than their oral administration, and since that time it has become almost axiomatic in many surgical clinics that jaundiced patients receive intravenous calcium by way of preoperative preparation. Walters,[4] of the Mayo Clinic, has developed a routine management for icteric patients, consisting of the daily intravenous injection of 5 cc. 10 per cent calcium chlorid solution for three days before the operation. The success of this method is reported to have been striking. Thus, Walters states that prior to the adoption of this management, of 29 fatalities after operations on jaundiced patients, autopsy revealed that in 16, death was due to hemorrhage, or at least a large amount of blood was found in the peritoneal cavity, and was considered to be a factor in the cause of death. Two years later Judd and Lyons[5] stated that "Although more jaundiced patients have been operated upon than in any previous year, the danger of postoperative bleed-

* This work was done in the laboratory of the University Surgical Clinic, Frankfurt-am-Main, Germany, director Prof. V. Schmieden.

ing has been practically eliminated." Four deaths are reported to have occurred in 150 operations on the common duct and of these "not one resulted from hemorrhage, in spite of the fact that many patients were deeply jaundiced at the time of operation. All of these jaundiced patients were given a careful preparatory treatment as outlined by Walters, and undoubtedly this is the reason many of them did not bleed." Beneficial results from the use of intravenous calcium have also been reported by Elving,[6] Maendle,[7] Laqua,[8] Schenck[9] and Löwenstein and Politzer.[10] Jansen,[11] on the other hand, found the coagulant effect of intravenous calcium extremely transitory in its action, a demonstrable effect being observed only for a half to one hour after the injection.

The use of calcium for its coagulant action, however, rests on no sound theoretical basis. It has never been satisfactorily demonstrated, for instance, that the delayed coagulability in jaundice is due to a calcium deficiency. King and Stewart,[12] it is true, found the blood calcium elevated from 16 to 20 per cent after ligation of the common duct, with a corresponding decrease in the tissue calcium. They assumed that the calcium unites with the bile pigments to form less toxic combinations, and that the diversion of the calcium from its normal rôle in coagulation, for this purpose was responsible for the delayed coagulability in obstructive jaundice. I have been unable to find confirmation of this work except that which may be indirectly induced from the experiments of Walters, who showed that the lethal dose of calcium in jaundiced animals was much greater than that in the normal. This, too, seemed to suggest the formation of a relatively nontoxic combination of calcium and bile pigments.

Granting the possibility that the lack of available calcium may play a part in the delayed coagulability of jaundice, it has never been shown that more than just a transitory rise in blood calcium can be obtained by the intravenous injection of its salts. Jansen, in the work quoted before, found that immediately after parenteral introduction of calcium, its excretion began and that the concentration in the blood reached the normal or below normal figure within one to two hours after the injection. The experiments of Bowler and Walters led to practically the same results. Small doses of the chlorid injected intravenously were excreted in a half to one hour; complete elimination of large doses (ten times the therapeutic dose) occurred within four hours. Heubner and Rona,[13] working with cats, found that two hours after the injection of large amounts of calcium salts, the concentration in the blood had returned to its original level.

In this connection it is interesting to note further, that tetany, with its greatly reduced blood calcium content, is not as a rule, associated with delayed coagulation or a tendency toward hemor-

rhage. Simpson and Rasmussen[14] studied the coagulability of blood after experimental thyro-parathyroidectomy, and found no change in coagulation accompanying the tetany so produced. In recent work Vines[15] has found that ionized calcium is not necessary to coagulation, that this fraction of the blood calcium can be precipitated without hindering the clotting process. Stuber and Focke[16] have further demonstrated that, contrary to the accepted idea, calcium is not essential to coagulation, and have succeeded in producing clots in the entire absence of calcium. They attribute to calcium only the unspecific action of bivalent kations, in furthering the precipitation of protein bodies.

In addition to its lack of theoretical support, there are certain definite objections to the intravenous use of calcium salts. The injection of a hypertonic solution into the blood stream is certainly an unphysiologic procedure and not without its dangers. An uncomfortable sensation of warmth is usually complained of, and more serious symptoms are not uncommon. Aside from possible toxic effects from the parenterally administered calcium (Leo[17]), local necroses have not infrequently been observed from its injection accidentally or otherwise into the subcutaneous tissues (Wright), (Campbell,[18] Seelig[19]).

In the parathyroid hormone, isolated by Collip[20] (parathormone, Lilly), we now have a new method of influencing the calcium content of the blood. By means of its use we can increase the concentration of lime salts in the circulating blood at will; we are able for the first time to induce and maintain a demonstrable hypercalcemia. If such a calcium increase has any virtue in rendering the blood more coagulable, this is a surer, safer and certainly a more physiologic method of attaining it than by the intravenous injection of concentrated solutions. If no change in coagulation can be demonstrated with a definite increase in blood calcium, then we can discard the method entirely, saving our patients the discomforts, as well as the dangers of the intravenous calcium administration.

Present Study. By way of answering this question, I have studied the effect of the parathyroid hormone on the coagulation time in a series of normal and icteric patients and animals, determining, too, the calcium level before and after the injection. I realize that this work will meet the same objection that applies to all others dealing with clinical studies on coagulation, namely, the question whether the clotting time *in vitro* is sufficiently accurate an indication of the tendency to bleed to warrant our accepting the conclusions derived as guides to our therapeusis. As stated above, whatever other factors may enter into the etiology of postoperative cholemic bleeding, in many such cases a very marked delay in coagulability can be demonstrated. Petren, Lee and White[21] and others who have compared the coagulation time and the tendency to bleed in

jaundice have found the two parallel, and are willing to accept their coagulation determinations as prognostic, at least as to the danger of serious postoperative bleeding.

Method. Recognizing the difficulty of accurately determining the coagulation time, I have selected the method which I consider to have the fewest possible sources of error (modified by Stephan after Fonio[22]), and have made a sufficient number of routine determinations in normal subjects, until I could be satisfied with the technique. In making the determinations, blood was drawn by venepuncture, using the cubital vein in the human, the leg vein in the dog and taking care that the needle entered the vein with the first thrust. The necessity of properly obtaining the sample cannot be too strongly stressed, for experience teaches that the clotting time may be shortened from 50 to 75 per cent by merely having to seek the vein in the tissues, permitting that much contact of the blood with tissue juices. Eight to 10 cc. of blood were withdrawn, 10 to 20 drops (10 in the dog experiments, 20 in the human) were placed in each of three watch glasses, and the remainder was permitted to clot in a clean, dry test tube to be used for the calcium determinations. The watch crystals should be of equal size, thoroughly washed and dried, rinsed with ether-alcohol and scorched in a gas flame directly before the determination, allowing only time enough for them to cool down to room temperature. Immediately after introducing the blood the glasses were rotated gently, and placed in Petri dishes containing moistened gauze, to eliminate the effect of evaporation. The glasses were then rotated at regular intervals, and the endpoint of clotting taken at that stage where the glass could be held vertically, without altering the surface of the mass. An average of the three readings was taken as the coagulation time. The endpoint is fairly sharp, and repeated determinations check closely with one another. A slight variation from day to day in the same subject was found, and considerable variation in different normal subjects. Insofar as was possible, the determinations were made at the same time of day, and all of the conditions maintained unchanged. The use of a thermostat was purposely avoided, to enable making determinations in the patients' rooms if desirable. The temperature, however, was noted in every case, and from the tables it will be seen that the difference in temperature at which the determinations in each experiment were made, rarely exceeded 1°. The clotting time by this method is rather long, averaging about twenty-five minutes in the case of the dog and thirty minutes in the human, at ordinary room temperatures. The long coagulation time is held to be an advantage, in that small errors become relatively unimportant. The blood calcium determinations were made by the Tisdall[23] modification of the Kramer-Tisdall method.

Experiments with Normal Animals. Dogs were used for the experiments. Daily determinations of calcium and clotting time were made for several successive days to establish the normal. Varying doses of parathormone were injected and control determinations made at different intervals. As a rule, repeated experiments were made in the same animal. A series of typical results is listed in Table I.

As will be seen, the serum calcium in the normal dog was found to be between 10 and 11.5 mg. per cent. In some cases excessive doses of the hormone were used, bringing, in the case of animal No. 1, the calcium to almost twice its normal value. The tabulated results show that even these great variations in the calcium level produced no change in the coagulation time of the blood.

Experiments with Jaundiced Animals. In a series of dogs operated upon under ether anesthesia the common duct was ligated and divided just proximal to the point of entry of the duct into the duodenum. To exclude the action of the gall bladder the cystic ducts were also cut between ligatures. The animals all became icteric, and studies of calcium content and clotting power of the blood before and after parathormone injections were made. A number of the results obtained are listed in Table II.

While in most cases some delay in clotting could be demonstrated following the operation, I was not able in any of the animals to produce the hemorrhagic diathesis of cholemia. This was due in part, at least, to the fact that the animals usually declined rapidly following the duct ligation, and died as a rule between the second and third week. In some instances this was due to ascending cholangitis and liver abscesses. In a few cases biliary fistulæ formed. In this series of animals, too, no constant change in the coagulability could be demonstrated with variations in the calcium level of the blood.

To determine the effect of calcium level on coagulation of human blood, studies were made before and after parathyroid hormone injection, in a small group of individuals with normal blood (Table III). Of course, relatively smaller doses of the extract were used and the control determinations were not made nearly so often. The results coincide with those obtained in the dog; the coagulation was not affected by elevations in the calcium content (Table III).

I had the further opportunity of carrying out the experiments in several patients with obstructive jaundice. As will be seen from Table IV, 2 of the number had high-grade jaundice of relatively long standing, with appreciable prolongation of the clotting time.

It was not possible to increase the coagulation power by varying the concentration of the blood calcium in this way, nor could any change in the general clinical condition be demonstrated.

TABLE I.—EXPERIMENTS WITH NORMAL DOGS.*

Experiment No.	Before injection.			Units of parathormone.	After injection.				After injection.			
	Temp., C.	Coag., min.	Ca.		Hours after injection.	Temp., C.	Coag., min.	Ca.	Hours after injection.	Temp., C.	Coag., min.	Ca.
1	23.5°	18	10.3	60	23	24.0°	19	19.6	46	24.0°	24	15.5
2	23.5°	18	11.2	40	24	23.5°	25	16.9	48	23.0°	26	13.0
3	24.0°	21½	11.2	100	20	24.0°	23½	16.3	44	25.0°	...	13.6
4	24.0°	20½	11.2	100	22	24.0°	18	15.6	48	23.0°	22	13.1
5	21.5°	17	11.0	80	25	20.5°	18½	13.6	48	19.5°	19	11.5
6	21.5°	17½	10.9	100	23	22.0°	15½	18.0	45	21.5°	20	13.2
7	21.5°	25½	10.4	100	18	21.5°	26	15.5	25	21.5°	24½	13.3
8	21.0°	26½	11.2	60	26	21.0°	25½	14.4	49	21.0°	25	10.3
9	21.5°	27½	11.2	80	26	22.0°	26	15.6	31	21.5°	26½	13.4
10†	21.5°	26½	13.4	50	18	22.0°	25½	16.9	30	21.0°	25½	13.4

* In all tables calcium figures are given in milligrams per 100 cc.
† In this experiment the effect of the hormone injection was pyramided upon a hypercalcemia from a previous dose of hormone.

TABLE II.—NONJAUNDICED PATIENTS.

Patient.	Age, yrs.	Diagnosis.	Before injection.			Units of parathormone.	Hours after injection.	After injection.		
			Temp., C.	Coag., min.	Ca.			Temp., C.	Coag., min.	Ca.
W. R.	21	Old thigh injury	21.0°	29	10.0	20	24	21.0°	29½	11.7
A. R.	49	G. C. arthritis of ankle	21.0°	35	9.6	40	22	21.0°	40	11.5
K.	23	Chronic osteoarthritis	21.0°	37	9.9	40	24	21.5°	43	11.0
W. S.	19	Old head injury	22.5°	32	10.5	60	22	22.0°	22	12.2
H.	52	Old ankle fracture	21.0°	28½	10.7	50	24	21.0°	27	11.2
W.	65	Elbow fracture	21.5°	39½	10.4	50	24	21.0°	41	11.0

TABLE III.—DOG EXPERIMENTS—AFTER LIGATION OF COMMON DUCT.

Experiment No.	Before operation.			Days after operation	Before injection.			Parathormone units.	Hours after injection.	After injection.			Hours after injection.	After injection.		
	Temp., C.	Coag., min.	Ca.		Temp., C.	Coag., min.	Ca.			Temp., C.	Coag., min.	Ca.		Temp., C.	Coag., min.	Ca.
1 . . .	23.5°	18	10.7	11	21.5°	34	10.9	40	24	22.0°	35½	13.2				
2 . . .	24.0°	20½	11.2	7	23.5°	29	10.9	50	24	23.0°	25	13.6	48	23.0°	22	12.3
3 . . .	21.5°	17½	11.0	5	20.0°	27	10.4	60	24	21.0°	27	15.2	50	20.5°	22	10.9
4 . . .	21.5°	17½	11.0	12	21.5°	22	10.6	60	27	22.0°	19	16.9	49	21.0°	22	11.6
5 . . .	21.0°	26	10.3	4	21.5°	26½	10.7	60	27	22.0°	27	12.6	49	21.5°	25	10.1
6 . . .	21.5°	17½	11.0	14	21.0°	22	11.6*	50	24	21.0°	22	16.4	48	21.5°	21	12.5
7 . . .	21.5°	26	10.3	6	21.5°	25	10.1	50	24	21.0°	26	11.8				

* Pyramiding effect from repeated hormone injections.

TABLE IV.—JAUNDICED PATIENTS.

Patient.	Age, yrs.	Diagnosis.	Duration and grade of jaundice.	Before injection.			Units of parathormone.	Hours after injection.	After injection.		
				Temp., C.	Coag., min.	Ca.			Temp., C.	Coag., min.	Ca.
A. S. . .	64	Common duct stone	High grade; 3 wks.	21.0°	42½	9.7	40	24	20.5°	46	10.5
M. . . .	45	Cancer of gall bladder	High grade; 5 wks.	21.0°	51	10.4	60	23	21.0°	65½	12.5
M. . . .	45	Cancer of gall bladder	High grade; 6 wks.	22.0°	47	10.7	60	23	22.0°	56	12.5
A. S. . .	64	Common duct stone; 10 days P. O.	Still jaundiced	22.5°	34	10.2	40	22	22.5°	42	13.7
F. S. . .	48	Common duct stone	Light grade; 8 days	20.5°	51	9.2	60	26	20.5°	52	12.2

Discussion. In these experiments there was considerable individual variation in susceptibility to the action of the hormone. In the case of the dog the effect was inversely proportional, roughly, to the size of the animal. Despite the fact that very large doses were used in some instances, producing very great excursions in the calcium level, there were, as a rule, no serious general reactions. In Experiment 1 (Table I) the animal was a small, young puppy. After a moderate dose of hormone the calcium was elevated from 10.3 to 19.6 mg. per 100 cc. of blood, an increase of over 90 per cent. At the height of the action the animal was visibly depressed and apathetic. No gastrointestinal symptoms, other than a loss of appetite were observed, and on the following day the animal appeared perfectly normal again. The human subjects were conscious of absolutely no general effect, and locally of only slight swelling and redness at the site of injection. In the icteric subjects no change in the general condition could be seen as a result of the increase in circulating calcium.

Although none of the patients or animals with jaundice presented the marked blood changes found in the hemorrhagic diathesis of cholemia, still a demonstrable delay in coagulation was usually noted in the dog, and an even greater one in each of the patients studied. In none of these cases could a change in the calcium content of the blood, such as King and Stewart reported, be observed. Nor, as stated above, was the clinical condition improved or made worse by increasing the available calcium in the circulating blood.

As the tabulated results indicate, in the four groups of subjects studied no constant change in the coagulation time of the blood could be demonstrated with variations in the calcium content as induced with the parathyroid hormone, even though in some cases very wide fluctuations in calcium level were noted. The observations were made, as a rule, about twenty-four hours after the hormone injection, to avoid any possible confusion from the nonspecific effect of a hormone injection.

Since the completion of this work the report has appeared of studies made by Cantarow, Craven and Gordon[24] on the same subject. The interest of these writers in the effect of parathyroid hormone on coagulation was stimulated by beneficial effects they observed previously in the control of hemoptysis by the use of the hormone in tuberculous subjects. They conclude, as a result of their experiments, that there is a definite decrease in coagulation time following the hormone injection. This discrepancy between the results obtained by these writers and my own was somewhat disturbing, but several possible explanations present themselves. In the first place, the dosage employed by these observers was very small, compared to those used in this work; so small, in fact, that, as a rule, no appreciable change in the serum calcium could be demonstrated. Furthermore, the determinations were made much

earlier after the hormone administration (ten to twelve hours after the second injection). Any change, depending on a nonspecific reaction to a hormone injection would be expected to appear during this period much rather than at the later time. Finally, it must be pointed out that the coagulation determinations were made by the Boggs method, by which a drop of blood for examination is drawn from a needle puncture wound of the skin. The very marked effect of tissue juices on the coagulation of a sample of blood has already been mentioned, and inasmuch as the degree of admixture of such juice with the drop of blood to be examined cannot be controlled when blood is obtained in this way, the accuracy of all such methods must be questioned. The coagulation time as determined by this method, too, is very short, and differences of clotting time are measured in seconds. The percentage of error in such determinations must obviously be greatly increased. These authors, too, could demonstrate no constant relationship between the coagulation time and the calcium level of the serum. They did find, though, that the greatest increase in coagulability appeared at the time of the highest level of whole blood calcium.

Conclusions. 1. Elevation of the calcium content of the blood by the injection of the Collip parathyroid hormone had no constant effect on the coagulation time of the blood in normal or icteric patients or animals.

2. No demonstrable changes in the serum calcium level as a result of common bile duct obstruction were observed.

3. A regular delay in coagulation was seen in the cases of obstructive jaundice studied.

4. No clinical improvement in the condition of icteric subjects could be seen following an increase in the available circulating calcium as obtained by the injection of parathyroid hormone.

5. From the results of these experiments it would seem that increasing the calcium concentration of the circulating blood has no virtue in diminishing the coagulation time, either in the presence or absence of jaundice.

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HYPERTENSION OF THE PULMONARY CIRCULATION.*

Its Causes, Dynamics and Relation to Other Circulatory States.

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Introduction. Although the blood pressure within the pulmonary artery cannot be measured, we realize that hypertension can occur in the lesser circulation. Hypertension of the pulmonary circuit has not heretofore been considered a clinical entity, and the term

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has been employed infrequently and only casually in medical literature. Usually the clinical syndrome has been confused with "pulmonary congestion," "insufficiency of the right heart" and more especially with arteriosclerosis of the pulmonary vessels. This concept probably explains some of the rarer diseases associated with cyanosis; for instance, most of the cases of Ayerza's disease, some of Giesbock's disease (cyanosis, hypertension, splenomegaly) and some cases of the Osler-Vaquez syndrome. The recognition of this type of hypertension is not only important from the standpoint of diagnosis, but from the point of view of circulatory dynamics, since a knowledge of the compensatory mechanisms involved will help to clarify many of our current ideas of circulatory disorders, and will aid us in understanding the mutual reactions between disorders of the greater and lesser circulation. In this paper, which should be regarded as a preliminary survey, I shall discuss the circumstances under which hypertension of the lesser circulation occurs, the circulatory dynamics involved, the clinical recognition of the disease entity and its relation to other circulatory states.

Circumstances under which Hypertension of the Lesser Circulation Occurs. We can only surmise by indirect evidence that hypertension of the lesser circulation must occur.

In previous papers[1,2,3,4] I have attempted to show that, as far as the greater circulation is concerned, intravascular tension is one, if not the main, cause of arteriosclerosis and that in hypertension vascular lesions occur earlier than the normal involutionary changes (decrescent arteriosclerosis). The hypothesis was advanced that arteriosclerosis must be conceived not merely as a disease affecting the arteries, but of the capillaries and veins as well, and that the "nephritis" associated with hypertension is part of a generalized arteriocapillary disease. Chronic nephritis and arteriosclerosis are genetically speaking, therefore, one and the same disease, and are but simultaneous reactions to the same physiologic factor, namely, intravascular tension.

The immediate cause of hypertension is unknown, and we doubt if any single cause will ever be found, but we do recognize some of the circumstances under which a persistent peripheral resistance arises. We have described individuals of certain psychic makeups (antithesis of the child) in whom hypertension is apt to occur. The hypertension of persistent Grave's syndrome, a malady in which psychic influences are predominant etiologically, also indicates that psychic influences play an important rôle in hypertension. The demonstration[5] that increased peripheral resistance, resulting from congenital narrowing of the arteries or stenosis of the aortic isthmus, brings about sustained hypertension and eventual arteriocapillary disease is likewise very significant.

The pathogenesis of the vascular lesions represented under the

term arteriosclerosis from hypertension remains speculative. We believe the process is entirely mechanical and in the broadest sense compensatory and regenerative. The lesions probably represent a combination of stretching of the tissues, imbibition of cholesterol bodies, replacement fibrosis and eventual hyalin and calcareous deposition, and compensatory hyperplasia of the elastic fibers, muscularis and intima (Jores[6]).

One of the proofs of the relation of intravascular hypertension to arteriosclerosis submitted in a previous article was the independence of arteriosclerosis in the greater and in the lesser circulations. It is noteworthy that this independence, a huge and striking experiment *in vivo*, should have been overlooked in all studies upon the etiology of arteriosclerosis. We pointed out that, generally speaking, when hypertension occurred in young or middle-aged individuals arteriosclerosis was seen in the arteries of the greater circulation, and not in the vessels of the lesser circulation; *per contra*, when a lesion existed which could cause peripheral resistance in the lesser circulation arteriosclerosis of the pulmonary vessels was present, while arteriosclerosis of the greater circulation did not occur. It is true that moderate grades of arteriosclerosis of the pulmonary artery may be found even when no cause for hypertension of the lesser circulation is present, but it is only found in very aged individuals (Ljungdahl[7]), and is, therefore, analogous to the decrescent arteriosclerosis of the peripheral circulation. Inasmuch as the intravascular tension within the pulmonary artery is only approximately one-sixth that within the aorta (Starling[8]), it is not surprising that decrescent arteriosclerosis of the pulmonary artery should occur at a more advanced age than the decrescent arteriosclerosis in the greater circulation. Pulmonary arteriosclerosis has little respect for age. It occurs in much younger individuals than arteriosclerosis of the greater circulation, having been noted even in infants.

As in the greater circulation, arteriosclerosis of the pulmonary circuit affects not only the larger vessels but the capillaries as well. The walls of the capillaries are frequently much thickened, forming veritable knobs within the alveolus (Figs. 1, 2, 3, 4), and they may even show hyalin degeneration. As a consequence of the increase in perivascular connective tissue, the lungs show induration. This, in my opinion, is essentially the pathogenesis of the so-called "Stauungsinduration;" in other words, this is an arteriocapillary fibrosis.

From the standpoint of morbid anatomy, the presence of arteriosclerosis in the pulmonary artery means that a hypertension of the pulmonary circulation is or has been present. In other words, from my observations arteriosclerosis of the lesser circulation is almost always secondary. The question as to whether a primary arteriosclerosis of the pulmonary artery ever occurs will be discussed later.

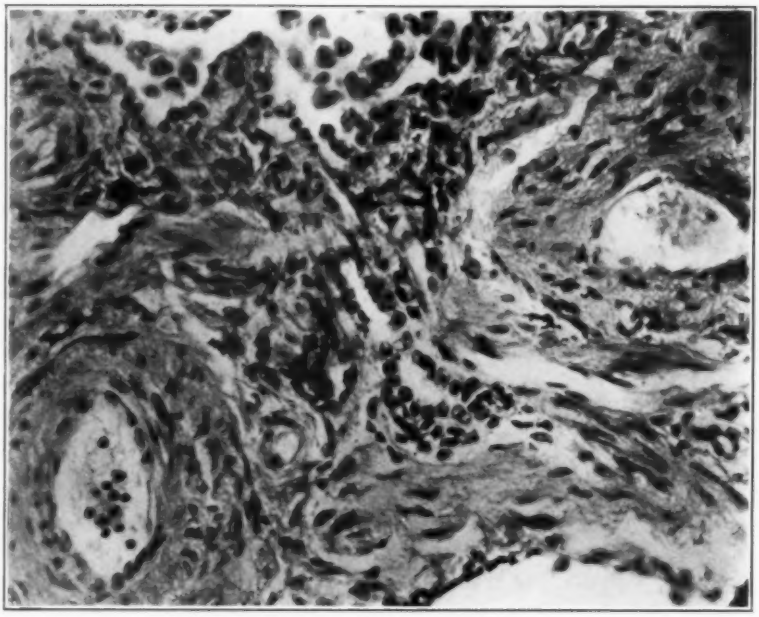

FIG. 1.—Section of lung in long-standing case of mitral stenosis, showing enormous thickening and sclerosis of arterioles with increase of interstitial tissue and reversion of alveolus to embryonal type; arteriocapillary fibrosis.

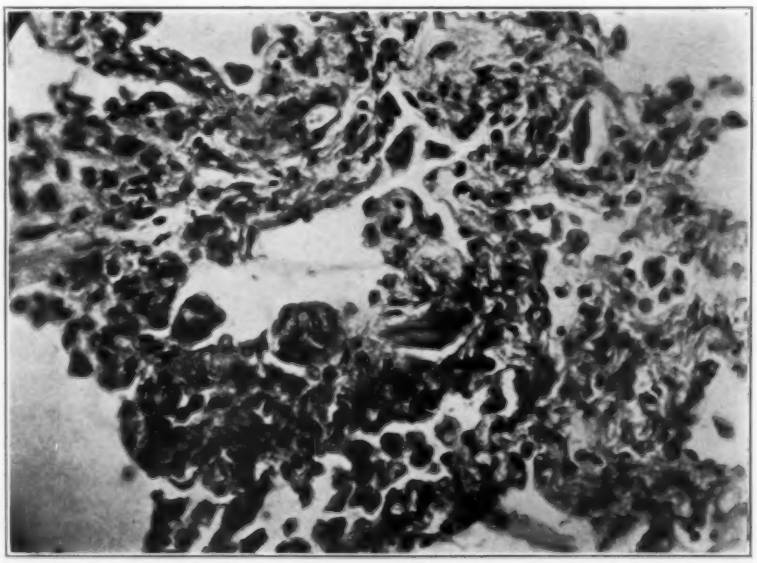

FIG. 2.—High-power section of the lung in a long-standing case of mitral stenosis, showing profound thickening of the alveolar capillaries and increase in connective tissue; arteriocapillary fibrosis.

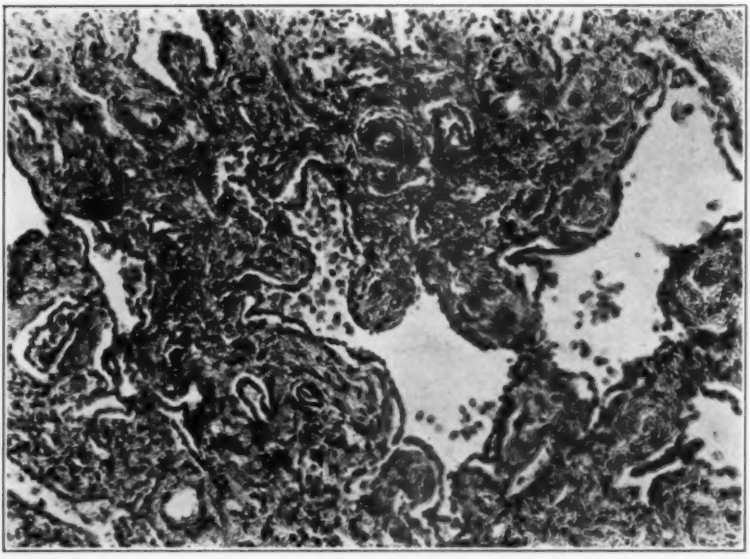

FIG. 3.—Section of lung from long-standing case of mitral stenosis, showing interstitial inflammation with reversion to embryonal type and thickening of the arterioles; arteriocapillary fibrosis.

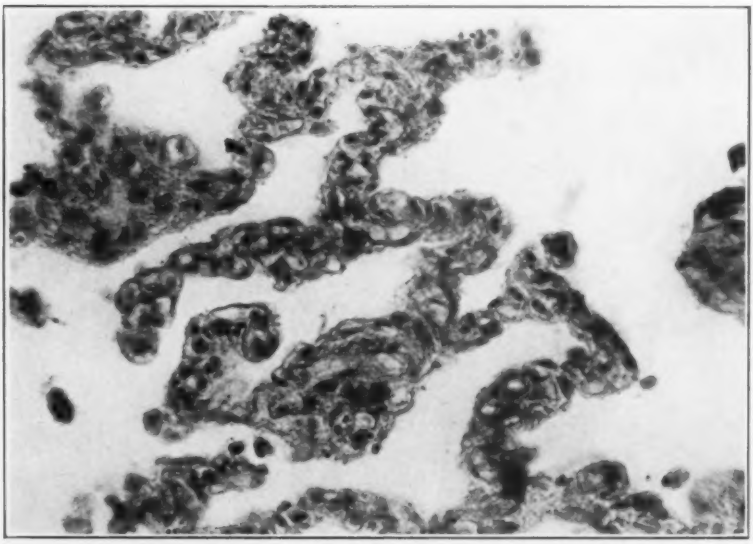

FIG. 4.—Section of lung from case of mitral stenosis, showing early or moderate lesion of arteriocapillary fibrosis, that is, dilatation and thickening of the alveolar capillaries with moderate interstitial change.

There may be other causes of arteriosclerosis, but no other cause has thus far been absolutely proven, that is, as far as the human subject is concerned. The experiments of Anitschkow[9] and more recently Newburgh and Clarkson[10], are often cited as indicating that a diet rich in cholesterol produced arteriosclerosis. As far as my study of the lesions of these observers leads me to believe, they have obtained *not* arteriosclerosis, but a lesion of the vessels characterized by a lipoid transformation of the intimal cells. There are no changes in the media or adventitia and there is no hyperplasia of the elastic fibers—a characteristic of human arteriosclerosis much emphasized by Jores. The lesions obtained by these authors are comparable to the familiar white or yellow fatty plaques well known in nursing children who are on a high-fat diet, or, in cases of lipemia, the result of a long-standing diabetes (Oppenheimer and Fishberg[11]).

The reader need hardly be reminded that syphilis does not cause arteriosclerosis in the sense in which this term is used (Jores), but an arteritis in which localization, infiltration and gummatous destruction of tissue play the dominant rôles.

In other words, lesions of the arteries are not necessarily arteriosclerosis. Certainly, from the standpoint of the study of human arteriosclerosis, the mutual independence of arteriosclerosis of the greater and lesser circulation indicates strongly that no poison, bacterial or otherwise, metabolic product or food substance can cause the lesion, because the same blood bathes both circulations.

With what lesions is arteriosclerosis of the lesser circulation associated as seen postmortem? In the order of frequency it has been observed with the following lesions: (*a*) *Mitral disease*, especially mitral stenosis. Most cases of long-continued mitral stenosis, no matter how young the patient, show a profound arteriosclerosis throughout the pulmonary artery. Posselt[12] found it in 47 out of 172 cases of mitral stenosis. Ljundahl found it in all but 1 of 37 cases. I do not recall its absence in many cases in my own observations. The greater the stenosis the more marked the lesion. The vessels of the greater circulation in such an individual are intact unless peripheral hypertension is or has been present. Pulmonary arteriosclerosis is present in mitral insufficiency, but for reasons to be discussed later the lesions are not as marked. (*b*) *Long-standing emphysema*, either primary (senile) or secondary (asthmatic). In Ljungdahl's series pulmonary arteriosclerosis was found in 7 of 21 cases. Here arteriosclerosis of both the greater and the lesser circulation may be found postmortem, for the obvious reason that emphysema is usually a disease of advanced life, so that not only is hypertension of the general circulation likely to be present, but the decrescent changes as well. (*c*) *In cases with marked diminution in lung volumes*, resulting from chronic tuberculosis, chronic interstitial pneumonia, new growths of the lung or mediastinum and so forth. (*d*) *In certain cases of kyphoscoliosis with marked deformity.*

Ljungdahl reports 4 out of 5 cases. (*e*) *In complete obliteration of the pleura.* (*f*) *In cases of patent ductus arteriosus.* (*g*) *In congenital lesions of the heart,* in which there is a communication between the right and left hearts, such as patent interventricular septum and open foramen ovale.

The common factor in these seven conditions is the increase in pulmonary vascular resistance. The peripheral resistance offered by a stenotic mitral valve is too obvious to require elucidation. The tension within the left auricle is much above normal. Mitral insufficiency likewise increases the tension within the left auricle, but the resistance, however, cannot be as great as in mitral stenosis, for the resistance offered by the systolic discharge of the left auricle against a tight mitral ring must be much greater than against an incompletely emptied left ventricle. It is for this reason that arteriosclerosis of the pulmonary arteries is, as a rule, less prominent with mitral insufficiency than with mitral stenosis. It is readily understandable why uncomplicated and compensated aortic lesions, whether stenotic or insufficient, are not associated with arteriosclerosis of the pulmonary vessels.

Emphysema probably causes an increased peripheral resistance to the flow of blood in the lesser circulation by the destruction of part of the capillary bed, as well as by compression and stretching of the arterioles due to the expansion of the alveoli (Cloetta[13]). In patients with marked diminution in lung volume, due to infiltration by chronic inflammatory disease, tumors and so forth, increased resistance is due to diminution in the size of the capillary bed. Ljungdahl found pulmonary arteriosclerosis in 2 of 3 cases studied. The changes were not as marked as in mitral stenosis. Hypertension within the pulmonary circuit can obviously only occur in kyphoscoliosis when the deformity is so marked as to cause compression or kinking of the pulmonary vessels (Vaquez[14]). In patent ductus arteriosus the increased tension is the result of the reflux of blood from the aorta into the pulmonary artery. Posselt collected 15 such cases; reports of this finding in the literature are common. In patients with congenital heart defect, in which the two sides of the heart communicate, the pulmonary arterial tension is obviously much raised, especially if the communication is between the ventricles and the shunt is from left to right. Posselt collected 6 cases of pulmonary arteriosclerosis associated with patent interventricular septum and some (a number not mentioned) with open foramen ovale. Watjen[15] recently reports an interesting case of pulmonary arteriosclerosis in a child, aged six months, with transposition of the vessels and a septum defect of the ventricles. This case illustrates, furthermore, that a hypertension need not necessarily be of long standing to produce arteriosclerosis. In Ljungdahl's series the earliest incidence of pulmonary arteriosclerosis was seven to eight months after the cause for the sclerosis appeared.

The pulmonary circuit is less able to withstand hypertension than the systematic circulation, because all the capillaries are constantly in use, while normally the systemic capillary bed is always particularly inactive (Krogh[16]). Furthermore, the collateral circulation between the pulmonary circulation and the aorta is entirely a capillary one between the pulmonary and bronchial arteries (Miller[17]), and offers little outlet for pulmonary pressure.

Changes in the Circulatory Dynamics Resulting from Hypertension in the Lesser Circulation. 1. *Increase in Venous Pressure.* Increased pressure in the pulmonary circuit may cause an increase of effective venous pressure (Wiggers[18]) in certain mechanical conditions. Normally there is a very nearly total expulsion of blood from the right ventricle with each systole, and as the ventricle is empty at the beginning of diastole, the rise in pressure which takes place from that time on will presumably start from zero. While the amplitude of a ventricular contraction depends primarily upon the so-called initial tension (which in the case of the right ventricle would be the resistance in the pulmonary circuit), this, of course, does not mean that an increase of initial tension would prevent the ventricle from completely expelling its contents. The initial tension, however, if continuously increased, will eventually stretch the ventricular walls beyond the point where a complete contraction is possible. The chamber now fails to expel its contents completely, and the residual blood produces more or less pressure at the beginning of diastole, depending upon the amount present. This dilatation of the right ventricle forces the right auricle to empty against a positive pressure, and an increase of venous pressure is the result. When the dilatation reaches the point of a definite incompetence of the tricuspid valve a tremendous rise in venous pressure becomes evident.

2. *Cyanosis.* The explanation for the cyanosis in hypertension of the lesser circulation is a complicated one and may be accounted for in a number of ways.

In the first place, the peripheral stasis and high venous pressure may account in part for the apparent cyanosis independent of changes in the arterial oxygen content of the blood (Goldschmidt and Light[19]). According to Danzer and Hooker,[20] the normal color of the skin is due to venous plexuses, and the blanching from pressure is produced by emptying of these vessels.

Furthermore, the cyanosis may be directly the result of the tendency to anoxemia due to changed bloodflow not only in the lung but also in the tissue capillaries. The anoxemia may be of the so-called anoxic type of Haldane, in which there is deficient oxygenation in the lungs or of the stagnant type due to decreased flow in the systemic capillaries, whereby there is a greater utilization of oxygen. The latter type obviously is aggravated when decompensation sets in. In both instances the amount of reduced hemo-

globin in the arterial blood is increased, a condition which Lungsgaard and van Slyke[21] have shown to be directly proportional to the degree of cyanosis.

When the congestion and stasis in the lung becomes marked, and especially when the fibrosis of "Stauungsinduration" has set in, there is a diminution in the vital capacity, with resulting anoxemia and cyanosis.

The erythremia and hyperplasia of the bone marrow so commonly observed is in all probability compensatory to the anoxemia.

Finally, aside from the factor of increased pulmonary arterial pressure, mechanical factors associated with the peripheral pulmonary resistances previously mentioned contribute to the production of cyanosis. In emphysema incomplete oxygenation is probably due to the well-demonstrated diminution in the alveolar area (Lundsgaard and Schierbeck[22]) and its common complication with bronchitis. In patients with advanced fibrosing tuberculosis, infiltrations and so forth one can readily understand that a greater or lesser proportion of bloodflow becomes unoxygenated, acting, therefore as a shunt. In patent ductus arteriosus and communications between the right and left hearts there is a definite shunt, so that considerable portions of blood do not pass through the lungs at all. According to Lundsgaard and van Slyke, approximately one-third of the blood must be shunted before cyanosis becomes manifest. It is interesting to observe in this connection that all evidence points to the fact (Lundsgaard and van Slyke[23]) that when the shunt is from left to right no cyanosis is present, but only when the shunt is from right to left. The probable explanation is that the cyanosis only arises when the congenital defect, either as the result of the continued mechanical forces or of an associated pulmonary stenosis, causes sufficiently increased pulmonary arterial pressure. This accounts for the late onset of cyanosis in congenital heart disease in which we can presume that originally the shunt must have been from left to right.

There is no doubt that hypertension of the lesser circulation alone may cause cyanosis, for the obvious reason that it is absent in uncomplicated aortic lesions, in which hypertension of the lesser circulation cannot occur, except in the terminal decompensated states. The presence of cyanosis, therefore, in association with aortic lesions usually means either a complicating mitral lesion or heart failure.

3. There is hypertrophy and dilatation of the right heart due to the resistance in the pulmonary circulation. With the increase in the diastolic pressure of the pulmonary artery the vessel dilates. These pathologic changes are observed roentgenographically, as evidenced in an enlarged pulmonary artery and in an enlarged right ventricle.

4. Owing to the increase in pressure within the inferior vena cava,

the outflow of blood through the hepatic vessels is hindered, the pressure within the portal circulation is increased and the parenchymatous organs within this circulation show engorgement. Clinically, there is enlargement and tenderness of the liver, rarely

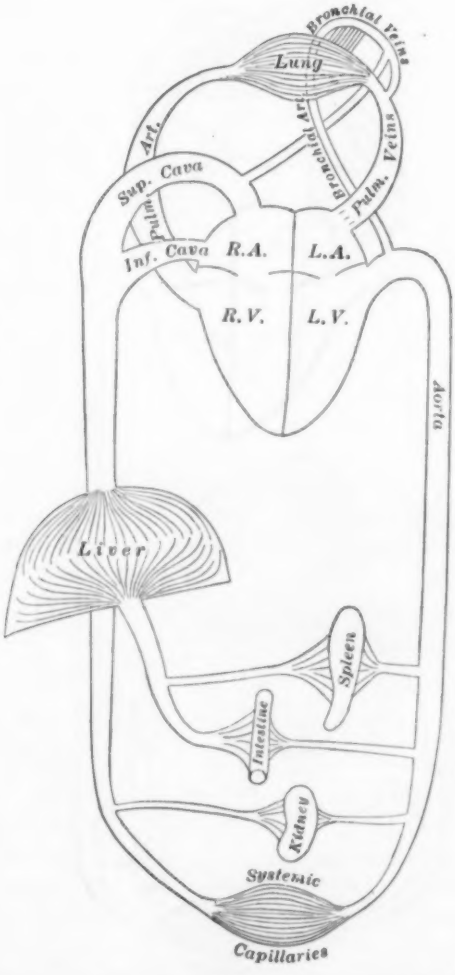

FIG. 5.—Schematic diagram, showing normal greater and lesser circulation.

of the spleen and a decrease in the urinary output with albuminuria. This congestion in the portal area is, in part, taken care of by the collateral circulation (esophageal, diaphragmatic and other veins), but never sufficiently to equalize the unequal distribution of pressure. As a consequence, ascites is extremely common in this con-

dition. Krogh has emphasized the importance of the liver as a double reservoir, to compensate for the increased venous pressure.

5. The venules of the upper thorax are prominent. This is seen especially in the later phases of intrapulmonary hypertension from

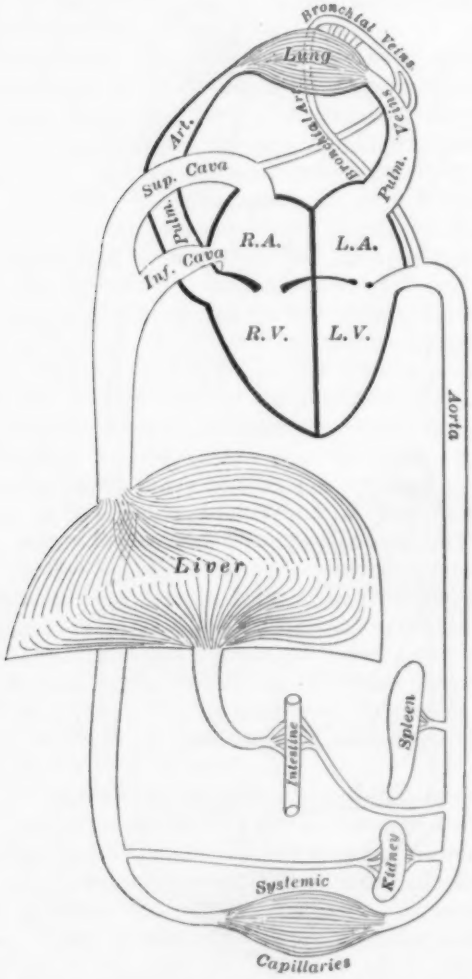

FIG. 6.—Schematic diagram, showing changes occurring in both circulations as the result of mitral stenosis. Note dilatation of the right heart and left auricle and of the pulmonary artery, and enlargement of the liver. The dark lines indicate hypertrophy of the muscular coats.

whatever cause. The explanation lies in the collateral circulation between the pulmonary and bronchial veins outlined above.

Renault[24] and Trunecek[25] have shown that in the pulmonary con-

gestion consequent on emphysema the blood expelled by the right heart into the lungs does not altogether return into the left auricle. Part of the blood returns by the bronchial veins into the azygos

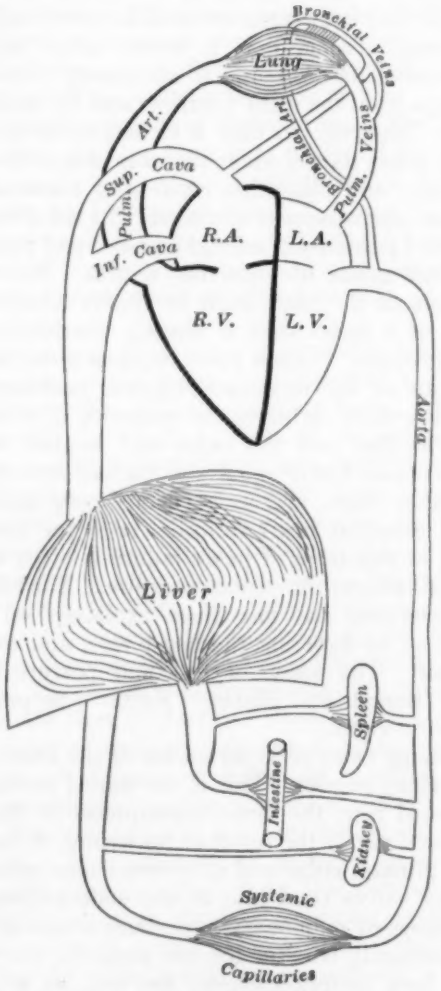

FIG. 7.—Schematic drawing, showing changes occurring in both circulations in emphysema. Note the dilatation of the right heart and of the pulmonary artery and of the liver. The dark lines indicate hypertrophy of the muscular coats.

veins and thence, owing to the anastomosis of the latter with the internal mammary veins, the pressure is transmitted to the veins of the pectoral wall.

6. A sustained and eventually progressive rise of the effective venous pressure and consequent rise in intrapulmonary pressure

must eventually influence the work of the left ventricle. This it does, according to Starling and his coworkers,[26] by stimulating the left ventricle to increase its stroke volume, which is in turn partially compensated for by lowering of the peripheral resistance. As long as the right and left ventricles are able to respond by greater contractions excessive congestion is never offset entirely. An increased left ventricular discharge is necessarily followed by an increased discharge from the right ventricle and an increase in pulmonary pressure (Wiggers), so that a vicious cycle is introduced which eventually takes its toll upon the muscular activity of both hearts; hypertrophy and dilatation ensue and eventually failure, with all the clinical phenomena of so-called right-sided heart failure.

7. With increased pulmonary arterial pressure and partial decompensation a certain grade of anoxemia results. The effect of a sustained anoxemia on the heart must inevitably interfere with the muscular action of a heart that is already overburdened by an increased venous return. Such a heart requires more oxygen than normal on account of the increased response necessary, but the amount falls a little short owing to the reduction of coronary flow, the result of dilatation and the rapid and weaker contractions (Hyde[27]; Marowitz and Lahn[28]). A still further reduction in cardiac efficiency takes place, and so a vicious cycle again becomes established with eventual heart failure. It is for these reasons that venesection in this form of heart failure is often an effective procedure, since it reduces the venous pressure. The effect of digitalis in decompensation has also been explained on this basis (Wiggers[29]), that is, by lowering the heart rate, and so increasing the coronary flow. The value of rest and posture in reducing venous pressure (Barach and Marks;[30] Eyster[31]) in part accounts for their therapeutic value.

8. In long-standing cases of hypertension of the lesser circulation tricuspid insufficiency results. This is the sequel partly of dilatation of the tricuspid ring, the direct consequence of the dilatation of the ventricle, and partly the result of thickening of the cusps due to the increased intraäuricular and intraventricular pressure. This thickening of the valves (and also of the endocardium) is never seen unless an increased pulmonary hypertension can be hypothetical. This is certainly true for the left ventricle, for corresponding thickenings here (arteriosclerotic) are not, as a rule, found unless general circulatory hypertension is or has been present.

The dynamic consequence of tricuspid insufficiency is not difficult to elucidate. The venous pressure is enormously increased, owing to the reflux of blood into the already overburdened right auricle; the cyanosis and venous dilatation become more marked; swelling of the portal organs becomes excessive; the positive venous pulse is transmitted through the hepatic vessels into the liver; the spleen enlarges so much as to become sometimes palpable; the con-

gestion in the kidney becomes so great that oliguria and albuminuria become more marked.

It is a curious fact that the cirrhosis of the liver associated with cardiac conditions nearly always follows conditions in which tricuspid insufficiency is present. One is tempted to think that the enormous venous pressures consequent thereto cause this increase in connective tissue (hepatic capillary arteriosclerosis). Studies in this direction will be made in the near future.

The Clinical Recognition of Hypertension of the Pulmonary Arteries. From the foregoing interpretation of the circulatory dynamics the clinical recognition by physical diagnosis of hypertension of the lesser circulation becomes manifest.

It is obvious that an accentuated second pulmonic sound is of primary significance in the recognition of this condition, at least in the stage before decompensation sets in and the pressure is lowered.

It is also obvious that a rise in venous pressure is an indication of hypertension of the lesser circulation and its measure is a guide to the degree of the pulmonary hypertension. When failure occurs it rises rapidly, and with a return of compensation it falls. The therapeutic value of lowering the venous pressure by venesection, digitalis, posture and rest has already been discussed.

Swelling and often tenderness of the liver are seen in such conditions as mitral disease and the terminal phases of emphysema, and the enlargement is a fair indication of the degree of failure present. Whether hepatic swelling associated with cardiac disease always represents a hypertension of the lesser circulation with its attendant increase in venous pressure, is a debatable question. From a mechanical standpoint this is probable. It is my impression that swelling of the liver is absent in uncomplicated aortic insufficiency or it is slight as compared to the inevitable enlargement in all forms of mitral disease and especially in mitral stenosis. Naturally, if heart failure in aortic disease, sets in left auricular pressure increases, hypertension of the lesser circulation sets in and a large liver results. The question of enlarged liver in aortic disease deserves more intensive study from this viewpoint.

It is significant that the Graham-Steell murmur is only found in marked cases of mitral stenosis with "back-pressure effects" (Wiggers[32]). In other words, it is probably a strong indication that hypertension in the lesser circulation is present.

When tricuspid insufficiency has set in, the clinical phenomena are too well known to demand portrayal. It is in this condition that venous tension is at its highest and hepatic and splenic swelling are greatest.

Subjectively, the one symptom that hypertension of the lesser circulation inevitably leads to is breathlessness. This has probably a direct relationship to the anoxemia.

In hypertension of the lesser circulation there is a strong tendency to infarct formation, especially in the later phases of the disease. This is accounted for by the slowing of the bloodflow and the sclerosis of the vessels. This and the intense congestion of the lungs account for the hemoptysis so common in this disease.

The Relationship of Other Circulatory Conditions to Hypertension of the Lesser Circulation. *General Vascular Hypertension.* In well-compensated hypertension there is no physical evidence of increased tension within the pulmonary vessels, nor on dynamic grounds is there any reason why there should be. Indeed, Ljungdahl and others have shown that pulmonary arteriosclerosis has no relation to hypertensive states in the general circulation. The compensatory effects of uncomplicated circulatory hypertension (essential) do not indicate any appreciable influences upon the venous pressure (Eyster).

In certain cases of hypertension, however, we all have noted clinical evidences of hypertension of the lesser circulations. Under what circumstances does this arise? It may occur in one of three ways:

1. *When the hypertension within the ventricle has caused a mitral stenosis of insufficiency, either by dilatation of the ring or by thickening (arteriosclerosis) of the valves.* This is a sequence of a sustained hypertension that is more frequent than generally supposed, and accounts for many of the obscure mitral lesions of middle and advanced life, especially mitral stenosis (Boas and Perla[33]). One reason why such an etiology has not been recognized is that, as the result of myocardial insufficiency or coronary closure, a previous hypertension becomes nullified. Such a drop in blood pressure is common.

2. *When decompensation ensues as the result of pure myocardial insufficiency.* When this happens the pressure in the left auricle becomes greatly elevated and the lungs become profoundly congested (Straub[34]).

3. *When there is an associated pulmonary lesion, such as emphysema or chronic fibrosing tuberculosis.* This association is not uncommon. These findings are in accord with those of various observers who have estimated venous tension in general hypertensive states. Our interpretation of the mechanism is somewhat different (Sewall;[35] Ratky and Klein;[36] Heloin.[37]

These physiologic responses explain in part, I believe, the difference between the so-called pale and red hypertensive patient, and why the pale hypertensive occasionally passes into the red phase. They also explain why the prognosis in the cyanotic hypertensive is much worse than in the pale type. The compensatory balance is extremely sensitive and, in my experience, blue hypertensives die of myocardial failure in a short time. As in certain cases of emphysema, this is one of the few conditions in which at postmortem arteriosclerosis of both greater and lesser circulations is found.

Relation of Coronary Disease to Hypertension of the Lesser Circulation. In pure disease of the left coronary artery uncomplicated by emphysema where compensation is good, there is no physical evidence of hypertension of the lesser circulation. Such hypertension can only occur when myocardial insufficiency of such a degree arises as to cause increased pressure within the left auricle or when mitralization supervenes. Under such circumstances the anginal symptoms may subside or even disappear because of the ensuing diminished diastolic pressure within the aorta, and the clinical picture is transformed to that of a pure myocardial insufficiency. It makes little differences whether the general circulatory tension has been previously high or low.

The Relation of "Primary" Pulmonary Arteriosclerosis to Hypertension of the Lesser Circulation. Does primary arteriosclerosis of the pulmonary vessels occur? I have not seen any cases of pulmonary vessel arteriosclerosis which could not be accounted for by one of the lesions causing increased pulmonary artery hypertension set forth above. Prof. Ludwig Pick, of Berlin, whose experience is huge, writes me that he also has never seen a case of primary pulmonary arteriosclerosis. Nevertheless, primary arteriosclerosis of the pulmonary vessels (exclusive of syphilis) has been reported, though rarely, and presents the syndrome of hypertension of the lesser circulation. A number of these are summarized in Ljungdahl's monograph. Curiously, in many of these "primary" cases a previous asthma, pleural obliterations and pulmonary indurations are mentioned. These cases obviously are doubtful as primary scleroses. A number of others, however (Mönckeberg;[38] Eppinger and Wagner;[39] Sanders;[40] Posselt[41]) showed no etiology. It is significant that in Ljungdahl's own case the sclerosed pulmonary artery and its branches, instead of being enormously dilated, as when it is affected by arteriosclerosis, was extremely narrow. This was also observed in the cases of Klobs[42] and Krutsch.[43] Ljungdahl believes that the narrowing was congenital and that the subsequent peripheral resistance caused an increased tension which, in turn, caused arteriosclerosis. This explanation is especially interesting to me in view of the fact that I reported hypertension and arteriosclerosis of the greater circulation in juveniles consequent upon congenital narrowing of the aorta and its branches. This mechanism probably excludes another group of primary pulmonary scleroses. There still remains a small number (presuming, of course, that they were well observed) in which no cause was determined. Eppinger and Wagner report 5 of their own and have collected 14 others. In attempting to explain the genesis of some of these cases, Posselt and, later, Hart[44] suggest an interesting mechanism. Their cases revealed narrowing of the pulmonary veins, a small left auricle and ventricle and a narrow aorta. These findings are also reported in the cases described by Sanders and Eppinger and Wagner. Posselt believed that the narrow pulmonary veins (the

result of a fetal endocarditis) furnished the necessary resistance to bring about pulmonary arterial hypertension, acting, therefore, like a mitral stenosis. It seems to me that Ljungdahl's interpretation is more reasonable. He believes that the hypoplasia is compensatory to the diminished inflow of blood consequent to the sclerosed pulmonary vessels. It must not be thought that this hypoplasia is peculiar to primary sclerosis. Zur Linden,[45] who reports his case as a primary sclerosis in a child, aged eleven months, strangely ignores an associated patent ductus arteriosus in the etiology.

At all events, one can say that primary arteriosclerosis of the pulmonary artery, if it exists at all, is extremely rare (excluding, of course, the decrescent variety) and can be practically ignored in the study of the subject.

The Relation of Edema of the Lungs to Hypertension of the Lesser Circulation. This is not the occasion to discuss the disputed subject of pulmonary edema. Clinically, it has various causes and the mechanism has been by no means settled. For our purposes it is merely necessary to point out that pulmonary edema has definite relations to pulmonary hypertension. It is a curious fact that pulmonary edema is very apt to arise in conditions in which one would expect the pulmonary resistance to increase rapidly, for instance, a very intense mitral stenosis, pulmonary embolism, rapid onset of left myocardial insufficiency from whatever cause (pneumonia, heart disease), thrombosis of the left auricle and so forth. Experimentally, also, pulmonary edema arises quickly after increasing the pulmonary resistance by ligating a branch of the pulmonary veins, after artificial emboli, obliteration of the left auricle cavity (Wiggers) or twisting of a pulmonary lobe so that the venous return is obstructed (Lambert and Gremels[46]). It is safe to say, therefore, that one of the causes of pulmonary edema is a sudden marked increase in tension within the pulmonary circulation.

On the other hand, recent work by Lambert and Gremels upon the heart-lung preparation apparently shows that pulmonary edema may give rise to increased pulmonary pressure. The increased resistance they ascribe "to the mechanical influence of the edema fluid on the pulmonary bloodvessels and to changes in the blood-vessel walls themselves."

Relation of Disturbances of Cardiac Rhythm to Hypertension of the Pulmonary Circulation. Without myocardial insufficiency a change in cardiac rhythm, exclusive of other complications, will not cause any change in the pulmonary circulatory resistance. When, however, myocardial insufficiency arises the mechanism is that already described. It is then either transient, being restored with returning compensation, or is more or less persistent, with the development of the physical signs of pulmonary hypertension.

Not all disturbances of cardiac rhythm, naturally, are of grave consequence. Fibrillation, flutter and a sustained tachycardia

(paroxysmal, Graves' syndrome) and block are probably the most serious. It is very significant that Eyster quotes instances of marked increase in venous pressure, with cyanosis, dyspnea, liver enlargement and albuminuria, in patients with paroxysmal tachycardia, associated with cardiac incompetence.

The Relation of Hypertension of the Lesser Circulation to Ayerza's Disease. In 1901 Ayerza described a symptom complex consisting of intense cyanosis, erythremia, enlargement of the heart, swelling of the liver and dyspnea. At autopsy arteriosclerosis of the pulmonary vessels was found which he believed was of syphilitic origin. Since this first description Marty,[47] Escudero,[48] Barloro,[49] Arrillaga[50] and others have elaborated on this syndrome, so that the term "Ayerza's disease" has acquired the dignity of a disease entity. There is no doubt that the description of this disease agrees entirely with that which we have set forth as occurring with hypertension of the lesser circulation. The question arises whether Ayerza and his followers are justified in ascribing the syndrome to syphilis of the pulmonary vessels. If this be so, then instead of changes in function causing anatomic alterations, as we maintain, anatomic alterations would cause changes in function. What evidence has been submitted that the arteriosclerosis of the pulmonary vessels is of syphilitic origin? As far as one can gather from the study of the papers of the above observers, the only evidence is that the Wassermann reaction is occasionally reported positive. Every clinician realizes that a positive Wassermann reaction may mislead in diagnosis. Many patients with gastric complaints have positive Wassermann reactions, but syphilis of the stomach is extraordinarily rare. In not a single instance is there a report showing Spirochæta pallida in sections of the sclerosed pulmonary vessels. Even Warthin,[51] whose persistence and ability for finding spirochetes in tissue is well known, fails to find the organisms in his well-studied case of "Ayerza's disease." Syphilis of the pulmonary vessels unquestionably occurs as Warthin[52] has shown, but, as far as one can gather from the reported cases, this symptom complex is not part of the clinical picture.

As a matter of fact, in most of the publications after Ayerza syphilis is no longer considered essential in the etiology. Both Barloro and Arrillaga regard the pulmonary sclerosis as secondary to pulmonary conditions. In fact, the latter says that in addition to syphilis any chronic pulmonary disease, such as bronchitis, pleural adhesions, tuberculosis or emphysema may give rise to the Ayerza syndrome, and states that the typical picture is preceded for many years by signs and symptoms of pulmonary disease. In Warthin's case there is a history of asthma and dyspnea for many years preceding the onset of the Ayerza syndrome. It is extremely interesting that Marty, who first published the term "Ayerza's disease," recognized the correct etiology of the disease, inasmuch

as he thought that increased pulmonary arterial tension was responsible in the etiology of certain cases of "cardiacos negros."

We conclude, therefore, that "Ayerza's disease" represents the common clinical syndrome associated with hypertension of the lesser circulation, that the rôle of syphilis in its etiology has by no means been proved, and that its position, therefore, as a new disease is without justification. If syphilis, on the other hand, is eliminated from its etiology the syndrome is one of the most common of clinical findings.

Summary. I believe that the following conclusions are correct:

1. Hypertension of the lesser circulation is common. It passes generally under the name of "pulmonary congestion" and "right-sided insufficiency," or "arteriosclerosis of the pulmonary vessels."

2. It is caused by any lesion that increases the peripheral resistance within the lesser circulation.

3. The most common causes are mitral disease, especially mitral stenosis, emphysema, whether primary (senile) or secondary (asthmatic), infiltrating lesions of the lung (chronic tuberculosis with induration, bilateral pleural synechiæ, chronic interstitial pneumonia, tumors), kyphoscoliosis, patent ductus arteriosus and communications between the two sides of the heart.

4. A sustained hypertension of the lesser circulation leads to arteriosclerosis of the pulmonary vessels. A "primary" arteriosclerosis of the pulmonary vessels, if it exists at all, is extremely rare. There is an independence in the incidence of arteriosclerosis of the greater and lesser circulations.

5. The compensatory dynamics following hypertension of the lesser circulation are described.

6. The physical signs of hypertension in the lesser circulation are those brought about by the compensatory mechanism. In the main these are: Increased venous pressure, accentuation of the second pulmonic sound, dilatation and hypertrophy of the right heart, dilatation of the pulmonary conus, cyanosis, dilatation of the superficial veins (especially pectoral), enlargement and tenderness of liver, lowered kidney function and infarction of the lungs.

7. It is the hypertension and not the arteriosclerosis that is responsible for this clinical syndrome. As in the greater circulation, it is the disturbed function and not the anatomic sequence that is at fault.

8. A transient (usually terminal) hypertension of the lesser circulation arises under a number of other conditions. In general vascular hypertension, hypertension of the lesser circulation may follow mitralization, when myocardial insufficiency sets in and when there is an associated emphysema. This explains, in part, the difference between the pale and the cyanotic hypertensive.

9. In left coronary disease hypertension of the lesser circulation arises only after myocardial insufficiency sets in.

10. The so-called "Ayerza's disease" is not a disease, but a syndrome developing from any lesion that causes hypertension and consequent arteriosclerosis of the lesser circulation. The constant relation of syphilis to this disease is not proven.

11. Edema of the lungs may either follow or cause hypertension of the lesser circulation.

12. Changes in cardiac rhythm cause hypertension of the lesser circulation only when myocardial insufficiency arises.

13. There is a likelihood that cirrhosis of the liver associated with cardiac disease is the result of the increased venous tension within the hepatic area and of an hepatic arteriocapillary fibrosis.

14. Hypertension of the lesser circulation may be the mechanism of the hitherto unsatisfactorily explained cyanosis in congenital heart disease.

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MYOSITIS OSSIFICANS PROGRESSIVA.

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Myositis ossificans progressiva is a disease characterized by multiple, if not generalized, ossification of the voluntary muscles of the body, without apparent cause. It is true that frequently a slight injury is connected with the ossification of the initial muscle involved, but this is by no means always the case. The disease is further characterized by a progressive course, with periodic exacerbations. The manifestations of the disease are congenital, or appear early in life. There is in most cases an associated anatomic anomaly of the great toes or thumbs in the form of microdactylia or brachydactylia.

The first recorded case of myositis ossificans progressiva was published by Freke,[1] in 1740, and the second by Copping,[2] in 1741; although Guy Patin,[3] in 1692, wrote of a woman who became as hard as wood all over. Bulhak,[4] in 1860, separated the progressive form from the isolated forms of the riding and exercise bone. The condition was given its present name by von Dusch,[5] in 1868. Münchmeyer[6] wrote the first exact description of the disease in 1869, and separated the condition from the big group of multiple osteomas. He also collected 12 cases from the literature. Helferich,[7] in 1879, observed a case of congenital ankylosis of the phalanges of the great toe, and of the thumb, associated with myositis ossificans. He was the first to associate the two conditions.

Since Münchmeyer[6] collected the first 12 cases from the literature in 1869, there have been a number of reviews of the literature from time to time by various authors. The number of recorded cases

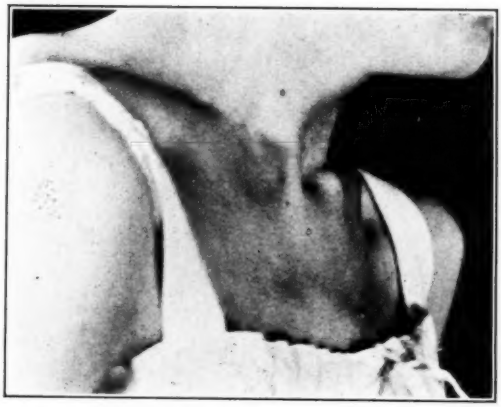

FIG. 1

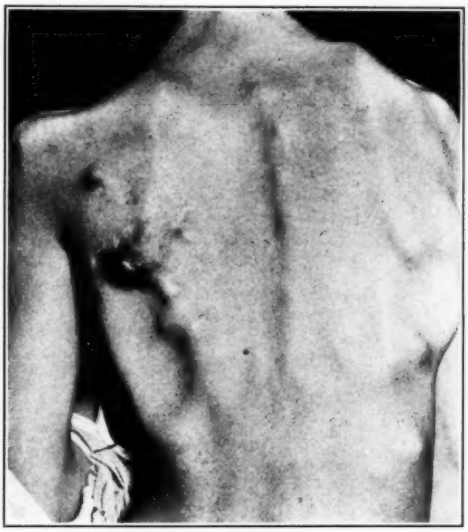

FIG. 2

FIG. 3.—Ossification of muscles of neck. Note also ossification of supraspinous ligament.

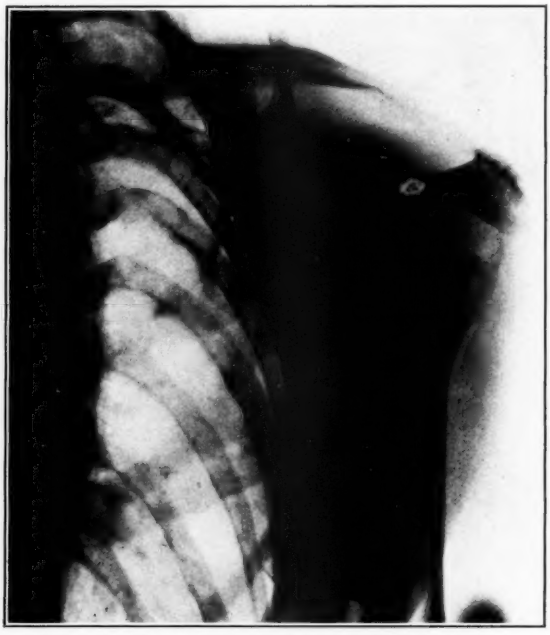

FIG. 4.—Ossification about right shoulder joint.

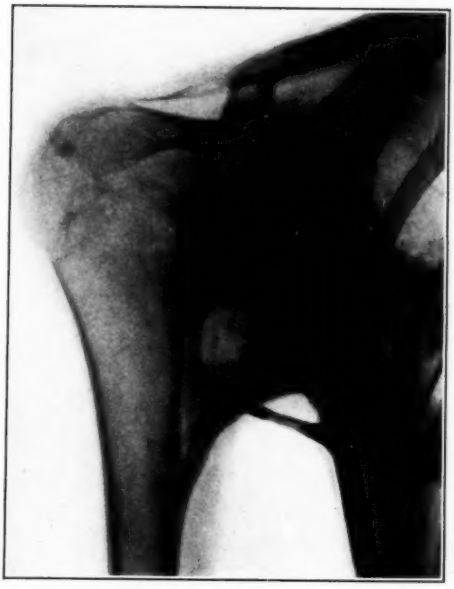

FIG. 5.—Ossifications about left shoulder joint.

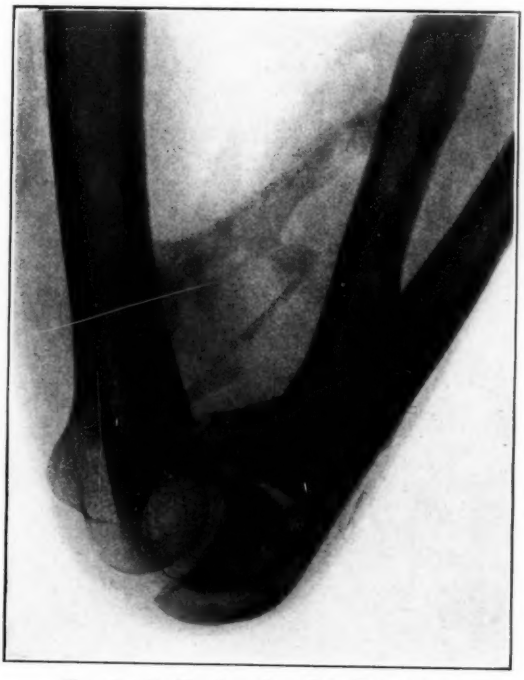

FIG. 6.—Ossification about left elbow joint.

FIG. 7.—Skiagram of hand, showing the markedly abnormal first metacarpal, and bony spines projecting from the third and fifth metacarpals.

FIG. 8.—Ossified bands connecting the ribs, and connecting the thorax with the pelvis.

FIG. 9.—Marked ossification of structures about right hip joint.

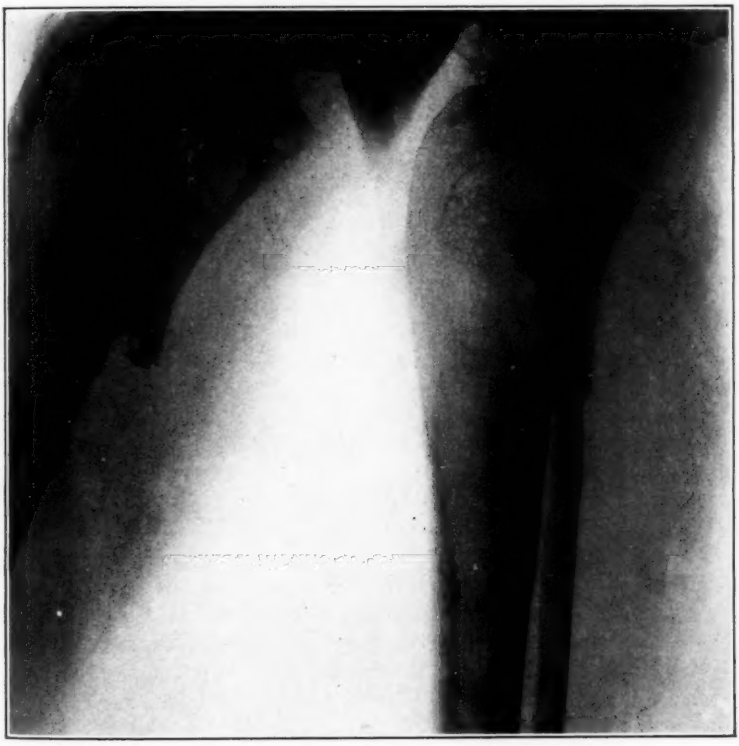

FIG. 10.—Spurs on posterior surface of tibial heads.

FIG. 11.—Skiagram of both feet showing abnormal first metatarsals, ankylosis of phalanges of both great toes, and bony bands connecting metatarsals of left foot.

has increased, until now, according to Magruder,[8] who has made the most recent tabulation from the literature, 133 cases have been reported, including his own. Among other recent reviews of the literature are those of Mackinnon,[9] Nutt,[10] and Rosenstirn.[11] The last-named author has gone into the subject most extensively.

To the cases already reported the present author wishes to add the following case:

Case Report. N. J., white female, aged seventeen and a half years, American extraction. Home in Wilmington, Delaware. The history was taken on January 20, 1926.

Family History. The patient comes from a good family. Her maternal grandfather and both of his brothers each had contractures of two fingers which developed late in life, and for no apparent cause. One cousin, on her mother's side, also, had the same condition. Her mother's half sister died at the age of twenty-two years, of some disease which her physicians said was generalized softening of the bones, but was not tuberculosis. The family history is otherwise unimportant.

Past History. The patient was born on August 17, 1908. Delivery was normal. She was a perfectly normal child until the onset of the present illness.

Present Illness. The present illness dates from July, 1917, when the patient was nine years of age. The first indication that there was anything wrong was that the patient told her mother that she could not bend down to lace her shoes on account of stiffness in her shoulder. Little attention was paid to this, but in September, 1917, the mother noticed a lump over the left shoulder blade. On the advice of the patient's family physician, a surgeon was called in, and operated, removing the lump from the left shoulder. The condition became worse after the operation, and very soon both shoulders were entirely stiff. A few weeks after the operation the neck also became involved and soon reached its present condition of absolute immobility. In December, 1917, the patient was taken to the Jefferson Hospital in Philadelphia and placed under the care of Dr. Da Costa. A small piece of bone was taken from the left shoulder for diagnosis, but no treatment was instituted. The patient remained in the hospital for five months and was told that nothing could be done for her. One year later she slipped on a rug, but did not fall, slightly spraining her right hip. Following this slight injury her right hip became absolutely stiff. There was no further progress of the disease until September, 1925, when she fell and scraped the left elbow and thigh. About ten days later stiffness of the left elbow, left hip and left knee commenced, and progressed rapidly until all three joints were immovable.

The patient did well in school and finished the first half of the third year high school in June, 1925. Owing to the rapid progress of the disease since her fall in September, 1925, she has not returned to school, it being very difficult for her to get around.

The patient has never menstruated.

Physical Examination. General. The patient is a slightly built young girl. Eyes, ears, mouth and nose normal. Heart and lungs normal. Abdomen normal except that the liver dullness begins above at the sixth interspace, and below extends almost to the level of the umbilicus in the midclavicular line. There are no axillary or pubic hairs. The left breast is about the size of half a small orange; the right one is not so well developed.

Special. The right sternocleidomastoid muscle is of bony hardness throughout its entire course. Superficial to this, there is a bony sheet, evidently platysma, which extends from the hyoid bone to the border of the right clavicle (see Fig. 1). These bony masses entirely prevent rotation of the head and have caused an unequal development of the structures of the face so that the patient's mouth is rather crooked. There is the very slightest motion of the cervical spine. Both shoulder girdles are firmly fixed to the underlying axial skeleton and are entirely immovable. There is very slight motion in the right shoulder joint so that the arm can be abducted a very few degrees. Motion is good in the right elbow joint and in the joints of the forearm and hand. The left shoulder joint is completely ankylosed. The left elbow is likewise immovable and the forearm is contracted in the position of acute flexion. Along the thenar border of the forearm, large bony masses are felt in the muscles. The hand is retracted in the position of acute dorsiflexion. There is no motion in the spine from the neck down. Numerous bony projections protrude from the entire back, including both the scapulæ and the ribs (Fig. 2). On deep inspiration there is no chest expansion except that the costal cartilages of the lower ribs flare out to a slight extent. The right hip is completely fixed. The right knee and joints of the leg have normal motion. There is the slightest possible amount of motion in the left hip joint. All the muscles of the anterior half of the left thigh are of stony hardness throughout their entire extent. The left knee is entirely fixed and immovable. The left ankle joint moves normally. Both great toes are much shorter than normal, apparently due to an abnormally short metatarsal. They give the appearance of the head of the metatarsal having been removed on account of bunion. The condition however, is a congenital one.

Roentgen ray Findings. Ossification of the muscles of the neck (Fig. 3). Ossification of the supraspinous ligaments of the cervical spine (Fig. 3). Ossification of the ligaments about both shoulder joints (Figs. 4 and 5). Ossification of ligaments of left elbow (Fig. 6). The first metacarpal of each hand is markedly abnormal, being much shortened and thickened and having a curious anomaly of the metacarpophalangeal joint (Fig. 7). There are also curious bony spurs projecting from the sides of some of the other metacarpal bones (Fig. 7). There are ossifying bands connecting the ribs with each other and connecting the thorax with the pelvis,

which have the effect of making a human straight jacket out of the axial skeleton (Fig. 8). The right hip is completely fixed by bony strands extending from the femur to the pubis, and the muscles of the outer half of the left thigh are ossified (Fig. 9). There are peculiar bony hooks projecting from the posterior surface of the head of each tibia (Fig. 10). The first metatarsals show the same sort of deformity as the first metacarpals. In addition, there is ankylosis and deformity of the phalanges of the great toes. There are also bony formations between the metatarsals (see Fig. 11). There is no abnormality of the sella turcica.

Urine Examinations. January 22, 1926: No albumin; no sugar; specific gravity, 1022; January 25, 1926: No albumin; no sugar; specific gravity, 1018. *Microscopic:* Epithelial cells; no pus, blood or casts.

Basal Metabolism Test. January 25, 1926 (Dr. Reinhoff): Plus nine.

Blood Report. January 20, 1926 (Dr. Pincus): Calcium, 10.3 mg. per 100 cc. of serum; phosphorus, 4.2 mg. per 100 cc. of serum.

The basal metabolism, blood calcium, and blood phosphorus are thus all seen to be within normal limits.

Statistics of Reported Cases. The incidence as to age and sex has recently been studied by Mackinnon,[9] who states that "in 116 cases in which the age of onset is stated, the first symptoms were noted during the first year of life in 19, and during the first five years in 79. Twenty-one more began before the age of eleven; 8 more before the age of sixteen; 7 between sixteen and twenty, and 1 after twenty. In 126 cases in which the sex is stated there were 75 males and 51 females." The 1 case mentioned in which the process began after twenty years is presumably that of Lexer,[12] in which the onset did not occur until the patient was thirty-four years of age. Lexer still had this patient under observation at the age of fifty, at which time he published his report.

The most common site of origin is in the cervical and dorsal region, from which it extends to the upper, and then the lower extremities.

The onset may be characterized by a pasty swelling of the part affected, with redness of the skin covering the area, and fever. The pasty swelling gradually hardens, as bone is formed. The swellings are sometimes painful, due to the occurrence of spontaneous hemorrhage in the muscles, a not uncommon phenomenon in these patients.

Defective development of the sexual organs or sexual functions sometimes occurs. In male patients this takes the form of rudimentary growth of the penis and scrotum, and in the female patients an absence of the menses.

Rosenstirn[11] reports a case of myositis ossificans progressiva occurring in a horse, and another in a dog. The case in the dog, it is interesting to note, was associated with microdactylia.

Rosenstirn's human case is the only one reported in which bone was found to be forming in the skin as well as the muscles.

Pathology. Lexer[12], following Münchmeyer, divides the progress of the disease into three stages as follows: (1) Doughy swelling of the soft parts, followed by (2) induration of the muscle—a state of fibrosis or connective tissue induration, and (3) ossification.

Careful microscopic studies have been made by a number of authors. De Witt[13] studied a case of early myositis ossificans in a man who died of tuberculosis. The microscopic picture was that of degenerating muscle, and leukocytic infiltration, with granulation tissue replacing the larger inflammatory areas. In the granulation tissue, there were irregularly branching and anastomosing trabeculæ of osteoid tissue. The osteoid tissue was "always found in the new granulation tissue, never in the old connective tissue, nor in the inflammatory tissue which is still undergoing retrograde changes."

Cause. We are still completely in the dark as to the cause of myositis ossificans. Many theories have been advanced, but none have been proven experimentally, and most of them are easily shown to be untenable. For a full discussion of these various theories the reader is referred to such papers as those of Rosenstirn,[11] De Witt,[13] Stempel,[14] Rohde,[15] Gruca[16] and Takasaki.[17] Mere mention may be made of some of them, as follows: That the condition is due to a retention of calcium in the organism owing to a faulty metabolism which failed to excrete its quota of lime; tumor (multiple osteomata); congenital predisposition toward ossification, of the intramuscular connective tissue, fascia and aponeurosis; extravasation of blood into the tissues; multiple exostoses; heredity; escape of synovial fluid from joints; borderline between inflammation and new growth; trophoneurosis comparable to progressive muscular atrophy and pseudohypertrophy of muscle; secondary to disease of the spinal cord; result of irritation of connective tissue through trauma or blood extravasation; inflammatory process of intermuscular connective tissue; cold; unsanitary surroundings; disturbance of embryonic development; atavistic influence; multiple small birth hemorrhages; articular rheumatism; scrofula; development of unused mesenchyme cells into osteoblasts; metaplasia of local connective tissue.

Lewis[18] points out that ossification of the abdominal muscles is not infrequent after operations on the stomach and bladder, and believes that the acid contents of these organs play a part in stimulating the fascia and muscle to bone formation. He[19] has suggested that the cause of myositis ossificans progressiva may be bound up with an excessive production of sarcolactic acid in the muscles.

In Rosenstirn's compilation of cases from the literature, there are 3 instances in which heredity was a factor. In 1 instance the condition was found in 3 successive generations, grandfather, father and three sons, all of whom showed the congenital finger and toe deformities. Rosenstirn thinks that both the microdactylia and the tendency to hemorrhage in these cases are evidences of imperfect development.

In the author's case also there is evidence of hereditary imperfections. The patient's maternal grandfather, his two brothers and a cousin all had contractures of two fingers. A maternal aunt also had some bone disease, the nature of which was unknown.

Painter[20] believes that whatever the underlying causative factors of the disease may be, the same factors are at work in the circumscribed traumatic form as in the generalized progressive type, but that in the latter case the tendencies responsive to the stimuli are more pronounced.

Diagnosis. There is no disease with which myositis ossificans progressiva could be confused. However, the circumscribed form of the disease frequently has to be differentiated from sarcoma, as pointed out by Finney[21] in 1909. The differential points are that sarcoma is more often found near the epiphyses, while myositis ossificans traumatica occurs more frequently along the diaphysis; the growth of sarcoma is steady and progressive, rather than spasmodic; in sarcoma the tumor never tends to become smaller, as it often does late in myositis ossificans; and, finally, the outlines of the bony tumor in Roentgen ray plates are not nearly so distinct in the case of sarcoma.

Coley[22] points out that pain seldom occurs early in sarcoma, and that the consistency of sarcoma is much softer than that of myositis ossificans. He reports a case of myositis ossificans of the lower end of the femur which became sarcoma six years later. He states that he is not sure whether the sarcoma was present, but dormant, from the start, and was stimulated to active growth by an operation which was finally performed because of evidences of growth in the tumor mass; or whether there was no sarcoma at first, but an eventual sarcomatous change in the myositis ossificans. He inclines to the latter view, but states that Ewing, who made the pathologic studies, was inclined to the former.

Paul[23] has recently reported a case of slow-growing, sclerosing osteogenic sarcoma associated with myositis ossificans. After removal of the tumor the myositis ossificans recurred but the sarcoma did not. He suggests that the "presence of the initial neoplastic lesion may have served as a stimulus for the development of previously latent, osteogenic change within the muscles and surrounding tissues." He thinks that it was a case of primary osteogenic sarcoma developing in a person who possessed a diathesis for bone formation.

Course. The disease progresses steadily, but periodically, over a long period of years. At first the patient's normal habits of life are not much affected, but as the disease progresses his activities are more and more curtailed by the disabling effects of the ossified muscles and ligaments. Death may finally occur due to ossification of the jaw muscles, which causes the patient gradually to starve.

Treatment. Numerous drugs have been used in the treatment of this disease. In many cases, excellent results have been reported

by the author first using the remedy, but, unhappily, others have failed to meet with the same success. The Roentgen ray has also been tried, but Rosenstirn states that in his case it stimulated rather than retarded the disease. Fröhlich[24] recently advocated a ketogenic diet. Noting that fractures in diabetic patients do not heal readily, it occurred to him that the production of a ketosis in myositis ossificans progressiva might have a favorable influence on the disease. Accordingly, he placed his two and a half year old patient on a diet poor in carbohydrate and rich in fat for one and a half years. Acetone bodies were present in the urine during the entire period of time. No more calcareous areas developed, and of the ones already present some disappeared and others diminished greatly in size.

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REVIEWS.

DISEASES OF THE DIGESTIVE ORGANS WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT. By CHARLES D. AARON, Sc.D., M.D., F.A.C.P., Professor of Gastroenterology and Dietetics in the Detroit College of Medicine and Surgery; Professor of Gastroenterology in the Detroit Post-Graduate School of Medicine; Consulting Gastroenterologist to Harper Hospital. Pp. 927; 174 engravings, 70 roentgenograms, 13 colored plates. Philadelphia: Lea & Febiger, 1927. Price, $11.00

THIS revised edition includes much new data and places emphasis, as it should, on digestive disturbances in their relation to bodily health in general. Before taking up the specific diseases of the gastrointestinal tract 13 chapters, 285 pages, are devoted to such subjects as the physiology of digestion, special methods of examination and various forms of treatment (including massage, hydrotherapy and electricity, as well as diet and medication). In this respect especially does this book have an advantage over the sections of our systems of medicine that cover the same subject. An abbreviation of some of the chapters with the omission of certain procedures that are now of only historical interest would have made for greater simplicity and conciseness and would not have detracted from the value of the text. T. M.

BASAL METABOLISM IN HEALTH AND DISEASE. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Associate Professor of Medicine, Cornell University Medical College, New York. Second edition. Pp. 431; 92 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $5.00.

THE second edition of Du Bois' book on Basal Metabolism in Health and Disease appears at a time when the first edition still held the foremost place in this field. With the added material and the bringing up-to-date which this book has undergone in this second edition, the book becomes preëminently the leader. It is not too scientific for practical workers and, on the other hand, covers in the most scientific manner the entire subject. It can be most heartily recommended. O. P.

A Manual of Materia Medica for Medical Students. By E. Quin Thornton, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College, Philadelphia. Second edition. Pp. 384. Philadelphia: Lea & Febiger, 1927. Price, $4.00.

The second edition brings this work into accord with the tenth revision of the United States Pharmacopœia. The volume offers a convenient manual of materia medica but differs in no important way from similar manuals. O. P.

Epilepsy: A Functional Mental Illness; Its Treatment. By R. C. Rows, M.D., Pathologist and Medical Officer, County Mental Hospital, Manchester; and W. E. Bond, M.R.C.S. (Eng.), Senior Medical Officer to the Minister of Pensions. Pp. 138. New York: Paul B. Hoeber, Inc., 1926. Price, $3.00.

An interesting work, though, owing to the death of one author, admittedly incomplete. "The use of the word 'functional' to indicate the underaction or overaction of the nerve elements, and the recognition that this will depend on altered nutrition, is the thesis we have attempted to establish." The treatment is one-sided. No mention of luminal, no consideration of diet, no avoiding of constipation, no occupational therapy. All appears to be embraced in "Explanation, Exploration, Reëducation." N. Y.

Medical Gymnastics and Massage in General Practice. By Dr. J. Arvedson; translated and edited by Mina L. Dobbie, M.D. Second edition. Pp. 284. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $2.50.

This excellent book describes in a concise and lucid manner the morbid conditions amenable to treatment by medical gymnastics and massage, the method of that form of therapy and the reason for its application in various pathologic conditions. A number of medicogymnastic prescriptions are given as examples. The technique of the various manipulations and exercises is not described in detail. For this information the reader, if necessary, is referred to textbooks dealing with that subject. The text in this edition has been increased and revised. The translation is well done.

The book shows throughout evidence of being written by a master in his chosen field. It should prove very valuable to the medical practitioner as well as to the nonmedically trained physiotherapist. J. N.

MATERIA MEDICA AND PRESCRIPTION WRITING. By OSCAR W. BETHEA, M.D., PH.G., Professor of Clinical Therapeutics, Tulane School of Medicine. Fourth revised edition. Pp. 498; no illustrations. Philadelphia: F. A. Davis Company, 1926. Price, $4.50.

THE book gives instruction in prescription writing together with the information about drugs necessary to prescribe them. The text has been revised to conform to U. S. P., X. Illustrative prescriptions are given for most drugs in many disease conditions. Some of these recall the therapeutics of the past rather than the present. The large amount of information contained will make the book valuable for reference. S.

AURICULAR FIBRILLATION. By J. G. EMANUEL, B.Sc., M.D., F.R.C.P., Physician to the Queen's Hospital, Birmingham; Consulting Physician to the Birmingham Free Hospital for Sick Children; Lecturer in Clinical Medicine, University of Birmingham, England. Pp. 31; 16 figures. Birmingham: Cornish Brothers, Ltd., 1926.

THIS little book embodies two Ingleby Lectures on auricular fibrillation delivered by the author in 1925. The reviewer questions the utility of such a book. It offers no important contribution to knowledge and will, therefore, be of little interest to the advanced student of heart disease. Although the subject is adequately covered to meet the needs of medical students and practitioners, it is equally well covered in books covering a much wider field of cardiology and, therefore, having a correspondingly greater sphere of usefulness. C. W.

THE TREATMENT OF FRACTURES: WITH NOTES UPON A FEW COMMON DISLOCATIONS. By CHARLES L. SCUDDER, M.D., Consulting Surgeon to the Massachusetts General Hospital; formerly Assistant Professor of Surgery at the Harvard Medical School. Tenth edition, revised; octavo volume. Pp. 1240; 2027 illustrations. Philadelphia and London: W. B. Saunders Company, 1926. Price, $12.00.

THE author of this book needs no introduction to readers on the subject of fractures. The fact that this is the tenth edition, the ninth being now six years old, is evidence enough of the value that the surgical profession has placed upon this work. This last edition is infinitely larger than any of the previous ones. It gives in minute

detail the present knowledge of the operative and nonoperative methods of treating fractures. Chapters on special features in fractures have been given to authorities on those subjects for their consideration. Such conditions as pathological fractures, bone repair, fractures of the maxilla and mandible, massage, anesthesia and anesthetics, birth fracture, all fall within this category. The text is profusely illustrated with the special attention to the detailed discussion of treatment and the associated appliances of retention.

The bibliography has been very carefully considered, and those features that have been recognized as valuable have been incorporated in the text. It is the most excellent production and should be recognized as the authority that it is, namely, a comprehensive, scientific and thoroughly up-to-date consideration of the entire subject of fractures. The author is to be congratulated.

E. E.

DEFECTIVE MEMORY, ABSENTMINDEDNESS, AND THEIR TREATMENT. BY ARNOLD LORAND, M.D. Pp. 340. Philadelphia: F. A. Davis Company, 1926.

A COMBINATION of the author's rather unconventional views on mental mechanics, insufficiently supported by evidence, together with useful hints on practical methods of improving the memory. Though written from the popular point of view, pathological causes of defective memory are included and scientific authorities cited.

E. K.

HUNTER TOD'S DISEASES OF THE EAR. Revised and rewritten by GEORGE C. CATHCART, M.A., M.D., Consulting Surgeon to the Throat Hospital, Golden Square, late member of the Special Aural Board, Ministry of Pensions. Second edition. Pp. 333; 87 illustrations. New York: Oxford University Press, American Branch, 1926. Price, $3.50.

THIS is a brief but decidedly well-written and easily understandable book on diseases of the ear for undergraduate medical students and general practitioners, on account of its brevity, many fine cuts and beautiful illustrations.

The chapter on anatomy is well written with many illustrations, giving a student a clear idea of the temporal bone. Diseases of the external and middle ear and their treatments, including the simple and radical mastoid operations, are well described and illustrated. Complications of otitic origin and Bárány's tests are only slightly touched upon, but sufficiently for beginners.

This is by far one of the best books on ear diseases published for students and general practitioners.

D. H.

MOTHER AND UNBORN CHILD. By SAMUEL RAYNOR MEAKER, Associate Professor of Gynecology, Boston University School of Medicine. Pp. 198; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1927. Price, $2.50.

THIS is an excellent manual regarding prenatal care. Especially to be commended is the brevity and simplicity of the sections on anatomy and physiology, and the wholesome common sense manner in which the whole subject is presented. The book is sufficiently simple to be read by the average woman and sufficiently thorough to supply almost any desired information to a prenatal patient.

P. W.

HISTOLOGICAL TECHNIQUE. By H. M. CARLETON, University Lecturer in Histology, Oxford University; Chapters VII and VIII, in collaboration with FREDERIC HAYNES, Demonstrator in Histology, Oxford University. Pp. 398; 17 illustrations. London and New York: Oxford University Press, American Branch, 1926. Price, $5.00.

IN this useful book are included methods, not only for preparing normal tissues, but also for differentiating morbid changes and identifying bacteria and protozoan parasites. A short account of the structure of the living cell from the modern physicochemical viewpoint is given first. The selection of the methods covers all the important standard ones, and these are described clearly step by step, with many hints which will be found useful not only to the beginner but also to the experienced worker. Under accessory methods of examination are found dark-ground illumination and histochemical tests for adrenalin, calcium salts, fats and other substances. Recent methods for showing mitochondria and the Golgi internal reticular apparatus are fully given. These and other excellent features combine to make this a most desirable book for the laboratory of normal or pathologic histology. W. A.

INTRODUCTION TO PHYSIOLOGICAL CHEMISTRY. By MEYER BODANSKY, University of Texas. Pp. 440; 40 illustrations. New York: John Wiley & Sons, 1927. Price, $4.00.

THIS book very adequately fulfils the need of a complete volume of physiological chemistry in a smaller text than is usually found necessary to use. The development is very logical and sufficient attention is paid to physical chemistry in conjunction with the metabolic aspects. The treatment is thorough but brief. The

clinical aspects are not neglected and its concise and convincing presentations should highly recommend it as a text of Biochemistry in medical schools. The accessibility of material is enhanced by the omission of laboratory experiments. W. K.

SOUTH AMERICA. By FRANKLIN H. MARTIN, C.M.G., D.S.M., M.D., LL.D., F.A.C.S., Director-General, American College of Surgeons. Pp. 435; illustrated. New York and Chicago: Fleming H. Revell Company, 1927.

AN interesting account of tours made through Central and South America and Mexico by several prominent surgeons, undertaken in behalf of the American College of Surgeons in 1920 to 1924. The descriptions of medical schools, hospitals and the prominent physicians and surgeons furnish sympathetic pictures of the countries visited and should fulfil its principal object of fostering a sound Pan-americanism and of helping to create more friendly relations between the professions of this continent and the Latin American countries. The vocabularies in the fifth section will be of value to anyone about to visit these countries. E. K.

HISTORY-TAKING AND RECORDING. By JAMES A. CORSCADEN, M.D., Associate in Obstetrics and Gynecology, Columbia University, New York. Pp. 78. New York: Paul B. Hoeber, Inc., 1927. Price, $1.50.

IN this volume of seventy-eight pages, including an index, is to be found much practical information, relative to the need for a definite technique in history taking, and as to the subjects concerning which the examiner should inquire. It has been said that good medical history takers are "born, not made." Certainly, the products of our present-day medical schools show but slight evidences of having been sufficiently trained in this matter.

The author devotes forty-five pages of his text to a description of the aims of a good history, and to methods of securing reliable information from the patient, or his relatives, no matter what difficulties are encountered in so doing. In the remainder of this little volume a list of terms, and an enumeration and analysis of symptoms, are set down. No advice as to the best way to cause hospital interns to employ a chirography which can be deciphered in a fair percentage of cases is offered.

This appears to the reviewer to be a useful volume, and one which the average hospital would do well to place in the hands of its resident staff. J. D.

THE TREATMENT OF CHRONIC DEAFNESS BY THE ELECTROPHONOIDE METHOD OF ZÜND-BURGUET. By GEORGE C. CATHCART, M.A., M.D., Consulting Surgeon to the Throat Hospital, Golden Square, late member of the special aural board, Ministry of Pensions. Pp. 88; 1 illustration. New York: Oxford University Press, American Branch, 1927. Price, $1.35.

THIS book deals with the treatment of chronic deafness, and otosclerosis by the electrophonoide method of reëducating the ears by means of an instrument which produces the sound of the human voice in all its registers, first described by Zünd-Burguet of Paris.

The claims the author makes by this method of treatment are marvelous if properly carried out, and should receive the attention of every otologist in this country. This book is worth reading and checking up. D. H.

THE SPECIALTIES IN GENERAL PRACTICE. Compiled by FRANCIS W. PALFREY, M.D., Instructor in Medicine at Harvard University Pp. 748. Philadelphia: W. B. Saunders Company, 1927. Price, $6.50.

IN the preface, it is stated "this book is an attempt to simplify the problem of the general practitioner in dealing with the specialties." To this end, there have been collected eleven articles, each by a member of the staff of the Medical School of Harvard University. Certain sections have been adapted directly from the material of courses in the Harvard Medical School. There is no doubt that there is a great need for such a work, but whether it is possible to present the necessary material in one volume is the problem. In the present instance, one is at first tempted to believe that this difficult goal has been achieved, but on more careful study one's initial optimism fails to be sustained. One finds no section on neurology and, on the other hand, an attempt is made to cover the subject of surgery in ninety pages. Of course, the different sections differ in value but when, one finds space devoted in the section on Surgery to a definition of wounds and again that one of the ninety pages is given up to the subject of repair of wounds, one cannot help but suspect that certain of the sections are too literally adaptations of undergraduate teaching. Minor points to be noted concern a reference on page 642 to the use of epinephrin in a 1 to 100 solution; on page 671 a statement that suppurative parotitis after surgical operation implies septicemia and on page 676 a statement that the blood changes in Hodgkin's disease are quite characteristic and that the blood shows the presence of "certain characteristic large mononuclear cells." The reviewer closed the book with a feeling of disappointment; it neither fills a place in undergraduate teaching nor does it prove itself quite adequate for the graduate in general practice. O.

SAVING EYE SIGHT AFTER MIDLIFE. By J. HERBERT WAITE, M.D., S.M. Pp. 48; 6 illustrations. Cambridge: Harvard University Press, 1927. Price, $1.00.

THIS book, meant primarily for the laity, may be helpful to the general practitioner in stimulating him to be on the lookout for the danger signs of failing vision after midlife.

The author found that a third of all the cases of blindness after the fortieth year were due to glaucoma.

To save eye sight after midlife, he says, remember:

1. A periodic examination by an oculist is necessary because of the insidious onset of degenerative disease of the eyes.
2. Cataract may be part of a process, indicating the presence of a deep-seated and serious disease of the eye.
3. Blindness from glaucoma can usually be held in check if the patient will coöperate with his oculist.

IMMUNITY IN SYPHILIS. By ALAN CHESNEY, M.D. Pp. 85. Baltimore: Williams & Wilkins Company, 1927. Price, $2.50.

THE author has performed a service for syphilology which is all too infrequent in medicine in general, in writing this admirably critical review of a very large accumulation of knowledge regarding immunity in syphilis. The scientific balance and dispassionateness of this discussion impresses one fully as much as its extent. On important points brief tabulations summarize what would otherwise require pages of reading in a foreign language. Such a summary placed in the hands of the progressive syphilologists of the country is a more valuable weapon in developing the modern treatment of syphilis than a new drug. J. S.

A TEXTBOOK OF CLINICAL NEUROLOGY. By ISRAEL S. WECHSLER, M.D., Assistant Professor of Clinical Neurology, Columbia University, New York. Pp. 725; 127 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $7.00.

THE author frankly states that he is giving a digest of neurology, so that anatomy, physiology and pathology are not specifically dwelt on. A chapter on psychometric tests shows admirable treatment. It is surprising so many pages are devoted to neuralgia when recent trend has been toward the restriction of that term. Most neuralgia is due to fibrositis—a subject not mentioned—and most of what remains is neuritis. Psychoanalysis is given serious attention, with more than 90 per cent of its usefulness accredited to Freud. One is

startled by the statement that the symptoms of neurasthenia "are directly the result of excessive masturbation," unless one bears in mind that in the Freudian sense pure neurasthenia is rare. Since it is believed that diseases of the ductless glands belong elsewhere, these receive but little consideration. This volume is different from others on the subject, and much of the difference is an improvement.

N. Y.

BOOKS RECEIVED.

The Religion Called Behaviorism. By DR. LOUIS BERMAN. Pp. 153. New York: Boni and Liveright, 1927. (To be reviewed later.)

Text-book of Bacteriology. By WILLIAM W. FORD, M.D. Pp. 1069, 186 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $8.50. (To be reviewed later.)

Mother India. By KATHERINE MAYO. Pp. 440, 41 illustrations. New York: Harcourt, Brace & Co., 1927. (To be reviewed later.)

Osler's Modern Medicine. Reëdited by THOMAS MCCRAE, M.D. Third edition. Volume IV. Pp. 1011, 111 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $9.00. (To be reviewed later.)

The Human Body in Pictures. By JACOB SARNOFF, M.D. Pp. 120, 190 illustrations. Brooklyn, N. Y.: Physicians and Surgeons Book Company, 1927. Price, $2.50. (To be reviewed later.)

Dengue. Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention. By J. F. SILER, MILTON W. HALL, and A. PARKER HITCHENS. Pp. 476, 8 illustrations. Bureau of Printing, Manila, 1926. (To be reviewed later.)

Segregation and Autogamy in Bacteria. By F. H. STEWART, M.A., D.Sc., M.D. Pp. 104, 7 illustrations. London: Adlard and Son, Limited, 1927. Price, 7 s. 6 p. (To be reviewed later.)

Overcoming Tuberculosis. By GERALD B. WEBB, M.D. and CHARLES T. RYDER, M.D. Pp. 81 and charts. New York: Paul B. Hoeber, Inc., 1927. Price, $2.00. (To be reviewed later.)

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Addison's Disease and Diabetes Mellitus Occurring Simultaneously.—ARNETT (*Arch. Int. Med.*, 1927, **39**, 698) reports upon a very interesting clinical complex, namely, the association of Addison's disease and diabetes mellitus. This report is based upon one of the very few cases that has been recorded, in which these two disorders have occurred at the same time in the one individual. It is quite possible that in the other cases that have been reported the diagnosis of one or the other condition was incorrect. The case reported, aside from its rarity, also illustrates the difficulty of treatment of the patient, who showed marked hypersensitivity to insulin and pronounced tendency to ketosis. The extreme sensitivity to insulin was undoubtedly due to the involvement of the suprarenal gland, the hormone of which produces a glycemic effect totally different from that of the islands of Langerhans.

Relation between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women.—It is somewhat of a shock to find that the generally accepted figures of the normal given in texts are based upon a very small number of blood counts made many years ago. Practically no figures are available of a goodly series of counts upon women upon which to base a standard of normality for this sex. OSGOOD and HASKINS (*Arch. Int. Med.*, 1927, **39**, 643) have made a study of 100 young women between the ages of eighteen and thirty from the point of view of the total red count and hemoglobin determinations and also the cell-volume determinations, with the average and range of variations in the average and corresponding

indexes. By exact, careful methods they found that the average red cell count in 100 women, apparently young in age, is 4,800,000. This is contrasted with an average count of 5,400,000 in men of the same age period. The total hemoglobin for 100 cc. of blood in young women is 13.7 gm., as contrasted with 15.8 gm. in men. The total volume of the packed red cells per 100 cc. of fluid averages 41 cc. in woman, as contrasted to 45 cc. in men. Color index, volume index and saturation index will average 1 in normal young adults when properly calculated and based on accurate estimation of cells, hemoglobin and cell volume.

Severe Chronic Glomerular Nephritis —In severe glomerular nephritis it is customary to depend upon associated findings of high blood pressure, enlargement of the heart and changes in the fundi to confirm the diagnosis. These findings, together with marked nitrogen retention, are usually considered sufficient upon which to base the diagnosis of involvement of the glomeruli with the kidney. Occasionally rare cases have been observed and reported in which some of these basic findings have been absent. BANNICK (*Arch. Int. Med.*, 1927, **39**, 741) recounts 2 cases, with autopsy, of patients who died apparently a nephritic death as a result of proven glomerular involvement of the kidneys and in whom hypertension, cardiac hypertrophy and retinal changes were all absent.

SURGERY

UNDER THE CHARGE OF

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Intrathoracic Newgrowths.—EDWARDS (*Brit. J. Surg.*, 1927, **14**, 606) writes that at present malignant disease arising in the chest, mediastinum, pleura or lung unfortunately rarely offers any hope of radical operation. There are, however, two types of malignant disease which offer reasonable hope of radical treatment—localized endothelioma of the pleura and the so-called alveolar carcinoma, as the latter arises in the neighborhood of the middle of the lobe. A series of 7 operable intrathoracic growths is recorded. Of these 6 have recovered and have apparently been cured. One patient in whom death occurred illustrates the possibility of primary lobectomy in suitable cases. The risk of damaging the intercostal vessels is shown, especially when rib resection is used as a method of approach. Last, the cases showed that intrapleural hemorrhage may occur, even in the presence of drainage, without giving rise to any external evidence. The value of operations

in more than one stage is shown in 2 cases. Endotracheal anesthesia should be used where the pleura is free, but gas and oxygen by the ordinary method is better where adhesions are present. The value of adequate Roentgen ray examination is emphasized. Where possible, artificial pneumothorax should be done, both as a diagnostic method and as a preliminary to operation because the operative shock of opening the free pleura is reduced to a minimum in its presence. Thoracoscopy, bronchoscopy, lipioidol injection and bismuth meal examination of the esophagus may all prove valuable adjuncts to diagnosis and to subsequent treatment.

Traumatic Rupture of the Bladder and Urethra.—STIRLING (*J. Urology*, 1927, **17**, 503) claims that injury of the urinary organs is relatively infrequently as compared to injuries in other parts of the body due to their position. However, since the advent of the automobile injuries to the urinary tract have been more common. Of 7 reported cases, 4 were the results of automobile or motorcycle accidents, 1 resulted from a stricture of the urethra, 1 was from falling astride a buggy wheel, while the seventh was due to a blow against the saddle horn while riding horseback. Early diagnosis and treatment has reduced the mortality from 88.7 per cent to less than 40 per cent in cases of rupture of the bladder. The triad of symptoms—tumor, bloody urine with inability to void is very suggestive of rupture of the bladder, especially if no urine is obtained on catheterization. Traumatic rupture of the urethra is characterized by inability to pass a catheter to the bladder, blood at the urinary meatus, with swelling in the perineum. If seen early and drainage is established within twenty-four hours the mortality is very low. All cases of injury to the urethra should be followed up to insure patency of the canal and sounds passed at intervals to insure the caliber of the urethra remaining of ample size.

The Comparative Value of Guinea-pig Inoculations in the Diagnosis of Renal Tuberculosis.—MORSE and BRAASCH (*J. Urol.*, 1927, **17**, 287) found that in 8 (17.7 per cent) of a series of 45 cases of proved renal tuberculosis, the guinea pig findings were negative. This discrepancy may be explained by the inherent defensive factor of guinea pigs, by fibrosis and encapsulation of the infected area of the patient and by the appearance of the bacillus of tuberculosis in showers, so that at intervals the urine may be free from it. In 109 cases of proved renal tuberculosis, in which one kidney was apparently healthy, guinea pig inoculation was positive in 18 per cent. The subsequent mortality and improvement in such cases is practically the same as in those with strictly unilateral involvement. Excretory bacilluria as a confusing element in the diagnosis of surgical renal tuberculosis is largely neglible for few reports, if any, can be accepted as definite proof that the bacillus of tuberculosis is excreted through a normal kidney. Ureteral reflux probably explains most of the positive findings in the remaining apparently healthy kidneys of this series. The diagnosis of renal tuberculosis should not be decided from guinea pig inoculation alone. Other laboratory or cystoscopic aids should be used to establish it. In order of importance, these are urography, microscopic study of catheterized ureteral specimens, cystoscopic data, clinical data and particularly examination of the genitalia.

Bismuth Absorption, Distribution and Elimination.—GRUHZIT, FENDICK and SULTZABERGER (*Am. J. Syph.*, 1927, **11**, 87) say that the rate of absorption, distribution in the body and elimination of a new soluble sodium bismuth thioglycollate has been studied. A rapid distribution of the bismuth takes place through the body, and it remains in the blood stream circulation for about seventy-two hours. At the end of about six hours analyses of organs showed that bismuth had reached every organ and every tissue in the body. The concentration of the bismuth in the various organs was about the same at the end of six hours as at the end of twenty-five days after the injection. The bismuth appeared to be deposited in the bone in higher concentrations than in other organs except kidneys and spleen. It appeared that the bone served as a storage place for bismuth. The absorption and distribution of bismuth in the body was about the same in all animals studied. The rate of elimination varied widely in different animals and was independent of dosage administered. It appeared that each animal had a rate which was characteristic only for that particular animal.

Preoperative Iodin Therapy in Toxic Goiter: Indications and Limitations.—GRAHAM (*Am. J. Surg.*, 1927, **2**, 354) states that the most favorable response to iodin therapy occurs in patients who have had no previous treatment. The quantity of iodin necessary to effect the maximum clinical improvement is determined largely by the size of the thyroid and the degree of active hypertrophy and hyperplasia at the time the iodin therapy is instituted. The best clinical index of the degree of hypertrophy and hyperplasia of the thyroid is the consistency and vascularity of the gland. Patients who have had iodin previously show the greatest variations in their response to its use as a preparation for operation. The presence of adenomas in the thyroid is not, *per se*, a contraindication to the use of iodin preliminary to thyroidectomy. Even though we do not understand and cannot satisfactorily explain all of the phenomena observed after the administration of iodin, its preoperative use in the surgery of toxic goiter is justifiable provided its limitations are not transgressed, namely, it is not curative and it is utterly futile to give further iodin therapy in the already overiodinized patient. The clinical indications of overiodinization are increasing consistency or disappearance of the thrill and bruit associated with an increasing basal metabolic rate and persistence or aggravation of the clinical manifestations of the diseases. The third and absolute limitation of iodin as a therapeutic agent in cases of toxic goiter is the presence of a normal or completely involuted thyroid.

Tumors of the Cecum.—ERDMANN and CLARK (*Ann. Surg.*, 1927, **85**, 722) claim that 48 cases of cecal tumor were studied and carcinoma was found in 37 instances, tuberculosis in 7, chronic inflammation in 2 and lymphosarcoma in 1, while 1 case was undetermined. Other tumors occasionally found are cysts, gummas, lipomas, tuberculomas, papillomas, cholesteatomas, leiomyomas and actinomycosis. The ileocecal region is the site of predilection for tuberculosis because of the right lymph supply. Three of the 7 tuberculosis cases were of the hyperplastic type without a demonstrable primary focus. The fourth

had an involvement of the right lung and the cecal growth was considered to be secondary. Three others were taken to be tuberculomas. The Friedrick resection was performed in all the tuberculous tumors with no mortality and symptomatic cure. The authors preferred this technique (Friedrick operation) for tumors of the right side of the colon, and consequently have performed this technique in 27 of the cases reported. This technique consisted of the removal of 10 to 12 inches of ileum, the entire cecum, the ascending colon and from one-third to one-half of the transverse colon, completed by an anastomosis of the ileum to the transverse colon, end to end being the choice. Only appendectomy was done in 3 tuberculomas. The cecum has a predisposition to malignant degeneration because of its physiologic and anatomic relationship. Regional glandular metastasis was found in 25 per cent of the cases. The ileocecal valve was involved in 48 per cent. The signs and symptoms most frequently found were pain, loss of weight, a mass and marked anemia. Roentgen examination was the most accurate aid in diagnosis.

PEDIATRICS

UNDER THE CHARGE OF

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The Treatment of Epilepsy in Childhood.—HELMHOLZ (*J. Am. Med. Assn.*, 1927, **88**, 2028) reports his experience of five years in treating epilepsy with the ketogenic diet. He has treated 144 patients. Twelve of these suffered from the symptomatic epilepsy complicating encephalitis and cerebral palsy. He found enough improvement to demonstrate that the treatment is worth a trial, and that the percentage of cures is decidedly lower than in cases of idiopathic epilepsy. Of his own patients, 2 are free from attacks, 6 are improved, and only 4 are unimproved. The number of patients with symptomatic epilepsy that he has treated is too small to allow any decision with regards to treatment, but the experience certainly warrants a trial. Of the 132 cases of idiopathic epilepsy, 17 were observed and treated six months prior to the report, and were not included in the tabulations. Five of the latter showed temporary improvement while under observation, 3 were unimproved, and the attacks of the remaining 9 were not frequent enough to permit conclusions regarding the results. Twenty-four cases were unclassified. In this group of patients, he included those who were free from attacks for a long period, and those suffering from a return of attacks, whose state of ketosis was questionable, and those for whom luminal was required along with the diet to control the attacks. A large number of these patients did not keep in touch with the clinic, and some of them improved while under observation, but did not attain a state of ketosis

at home, and these cases were also not considered in the tabulation. Ninety-one patients stayed on the diet long enough to give a different idea of the effect of ketosis on the number and severity of convulsions. The diet did not seem to have produced a therapeutic effect in 42 cases of 46 present. Some of the children made temporary progress, but it was soon evident that the diet alone was not of great value. In 12 of the cases, there was a question of the ketosis attained when the patient returned home, but in the others ketosis was applied to produce a positive reaction of the urine with ferric chlorid according to Gerhardt's test. Of these 42 patients, only 30 were having attacks frequently enough so that the effect of ketosis could be noted while they were under observation at the clinic, and 14 of this number were temporarily improved, and 12 indicated early that the diet was ineffective. Forty-nine patients of 54 present were differently benefited by the diet. In some cases the number of attacks were markedly reduced and the intervals between them lengthened. The convulsions in the grand mal attacks were decreased in severity. While this treatment improves more than half of the cases, it does not benefit all cases alike, but in some of the cases that were not improved permanently, a temporary benefit was observed. It would seem that in these severe cases a therapeutic diet should be tried.

Pyopneumothorax in Infancy.—JOHNSON (*Am. J. Dis. Child.*, 1927, **33**, 740) states that pyopneumothorax may complicate pneumonia in infants, by coming on insidiously and spontaneousy, and is recognized only by careful and routine physical examination. It is probably not as rare a condition as the literature would indicate, but it is not recognized in many cases. The cardinal symptoms, tympany, coin sound, and succussion, were present in about half of the cases. The coin and succussion tests were usually elicited on the third day, after the onset of the pyopneumothorax. Diminished breath sounds, or their absence over an entire lung, with limitation of expansion on the same side are the most suggestive physical signs. The amount of fluid in pyopneumothorax, in infants is nearly always much more than is anticipated. Roentgen rays, taken with the patient in an upright position, always show the presence of air. All the 10 patients of this series probably had pleuropneumonia from the outset, and the pyopneumothorax was caused by a ruptured subpleural abscess. The similarity of the conditions found in 3 autopsies was striking. All 3 cases showed rupture of the lung in the upper lobe, and a thick pleural exudate with interlobar adhesions, collapsed lungs with one or more abscesses and bronchopneumonia. Resection of the ribs is the operation of choice, even though there are no signs of fluid.

Infantile Convulsions.—THOM (*Am. J. Physch.*, 1927, **6**, 613) reports from the statistics that show that infantile convulsions occur 67 times in every 1000 cases or about 1 in every 14 cases. In 265 unselected cases, the data of which were collected in a house-to-house canvass, 29 per cent of the patients were either mentally retarded or epileptic. There was little or no relation between the exciting factor of the first convulsion, that is, whether it was associated with trauma, gastrointestional upset, or an acute infection, the likelihood of any convul-

sions persisting, or the child's intellectual development being impaired. Of these 265 patients 42 or 16 per cent were mentally deficient and 35 or 13 per cent continuing to have convulsions. The number of mental deficiencies and epileptics was almost twice as great in these cases in which there was no apparent existing cause for the first convulsion. Those cases in which the convulsions occurred without any apparent exciting cause were invariably more significant and the prognosis should be more guarded than in cases in which the convulsions are associated with a definite cause. In a fairly large group of cases the convulsions are only a symptom of unstable nervous system, which is unable to withstand the ordinary stresses to which the normal child is subjected. There is, undoubtedly, a fairly large group of convulsive disorders in children in which the convulsions are symptoms of undiagnosed meningitis or encephalitis, which leaves behind irreparable damage to the nervous system. The convulsion itself will not associate with any devastating disease such a meningitis or encephalitis, but it may produce injury from which the brain never recovers. The convulsions associated with rickets and tetany may leave behind very different damage to the nervous system The author feels that if the infantile convulsions associated with rickets, gastrointestinal upset and acute infection were looked upon more seriously, and a greater effort was made to prevent other occurrences during early life each epilepsy and mental deficiency might be prevented.

The Chemical Composition of Colostrum and Early Milk.—LOWENFELD, WIDDOWS, BOND and TAYLOR (*Biochem., J.*, 1927, **21**, 1) stated the chemical composition of milk for the first fourteen days of lactation. They found that there was a difference between the milk of primiparas and multiparas, with regard to the relation during the early days of fat and protein. The protein and ash content of the milk vary very irregularly, according to the day of lactation, being very high in primiparas, less though in multiparas on the second and third days, and fall rapidly during the first week to reach an approximately normal level. The sugar content varies also according to the day of lactation, but not inversely as the protein and less regularly. It is at its lowest in the early days and rises to a normal level by the end of the second week. The fat content varies only according to the physical condition of the breast, and actual extraction, and not in relation to the day after delivery. The general behavior of fat in primiparas is reversed in the first days of lactation. The calcium content varies up to the fifteenth day among individual women, but not according to any factors concerned with individual lactation, and is not influenced by factors local to the breast. There is some possibility that the protein content of the milk rises slightly at the end of a single feeding. The difference is greater when the samples are taken in relation to an actual feeding, than when only the first and last portions of an artificially emptied breast are considered. The lactose content of the milk seems to be higher at the beginning than at the end of a feeding.

Ultra-violet Radiation from Sunlight and Incandescent Lamps.—BUNDESEN, LEMON, FALK and COADE (*J. Am. Med. Assn.*, 1927, **89**, 187) studied the rays of the sun and from lamps. They found that in Chicago comparatively little ultra-violet radiation of known physiologic

significance could be found in the sun's spectrum during the winter months. They felt that the ultra-violet rays are absorbed to a marked degree by the smoke in the atmosphere, and, on the other hand, they found that incadescent lamps of 300 watts emitted radiations in the ultra-violet phase which are of different physiologic interest. As a result of their studies they agree with the reports of former investigators as to the relative permeabilities to the ultra-violet rays of window glass and certain window-glass substitutes they have studied and will report subsequently the relationship between the seasonal variations of the solar spectrum and morbidity and mortality.

OBSTETRICS

UNDER THE CHARGE OF

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Clinical and Experimental Studies on the Toxemias of Pregnancy.—From a clinical and experimental study, STANDER (*Am. J. Obst. and Gynec.*, 1927, **13**, 551) repeats his previous classification of: (1) Eclampsia; (2) preëclampsia; (3) chronic nephritis, complicating pregnancy; (4) eclampsia, superimposed upon nephritis; (5) low kidney reserve. Preëclampsia differs from eclampsia only insofar as the patient has no convulsion or coma, and that the disease may be of a milder type; it occurs in less than 5 per cent of all toxemias. The systolic and diastolic blood pressures and the amount of albumin in the urine graphically charted convince one of the remarkable similarity between eclampsia and preëclampsia. In chronic nephritis impairment shows in the low reserve to meet the extra demand of pregnancy. Eclampsia superimposed upon nephritis is a very rare type of eclampsia, being a combination of eclampsia and chronic nephritis. The blood chemistry in a large series of cases over the past four years shows: (1) A high uric-acid content; (2) an increased lactic acid; (3) a tendency toward hyperglycemia; (4) a decreased CO_2-combining power; (5) with no increase in the nonprotein nitrogen, but sometimes a definite increase in the urea nitrogen. These blood changes are strikingly similar to the changes in blood chemistry occurring in an experimental anesthesia in 50 normal dogs, and differ markedly from the changes both in blood chemistry and pathologic lesions produced by the injection of either histamin or albumose. The changes are similated by an anoxemia. In the treatment of eclampsia morphin has a double value, as a sedative and also, of 8 hypnotics examined, it alone definitely raised the CO_2-combining power. Magnesium sulphate intravenously and subcutaneously produced a lowering of the CO_2-combining power and a slight increase in the blood sugar and may do no harm in eclampsia. The high diastolic blood pressure in eclampsia may be a protective measure

essential to elimination and contraindicates venesection. Insulin with a protective dose of glucose has proved to be satisfactory therapy in these cases and local and spinal anesthesia preferred to a general anesthesia, for they had no effect upon the blood chemistry in normal or eclamptic cases.

Indications and Technique of Cesarean Section.—The question of Cesarean section receives considerable discussion in this article by LULL (*Am. J. Obst. and Gynec.*, 1927, **13**, 633). He considers the indications for this operation have justifiably increased in recent years, but the borderline or elective section still offers more chance for unwise decisions than any of the problems presented to the obstetrician. Among the conditions in which the operation seems justifiable are placenta previa, premature separation of a normally situated placenta, certain types of toxemia of pregnancy, cardiac diseases, tumors of the vagina and uterus, other obstructive tumors, atresia of the birth canal, dystocia following operations for relief of retrodisplacements and some malpositions of the fetus. The fact that women who, having had one section previously, have given birth to other children spontaneously is not a criterion that it is safe to allow any woman who has had a previous section for a temporary indication to attempt labor in succeeding pregnancies. The decision in this type of case is often difficult. When performed, the operation is most satisfactory a few days before the estimated date of labor or within a few hours of its onset, under the ordinary preparation for any abdominal section, but omitting the usual hypodermic of morphin and atropin. Ether is probably most satisfactory of the general anesthetics, and the author prefers local to spinal anesthesia. He uses the classic incision, eventrating the uterus after the delivery of the child, and no longer packs the uterus. Absorbable sutures (No. 2 chromic 40-day catgut) are used to get careful muscle approximation and peritonealization of the wound. Supravaginal hysterectomy is done in cases potentially infected, in patients with tumors of the uterine body and in some cases of premature separation, in which it is found that extensive disintegration of the uterine muscle has invoked atony of the uterine musculature. In infected cases one may choose between straight section, with hysterectomy and so-called extraperitoneal operation of De Lee. The author considers sterilization justified at the time of a second section.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Mastoid Infections in Infants.—Until recently, a mastoiditis requiring operation was rarely diagnosed in infants except on the basis of such external signs as postauricular redness, swelling or subperiosteal abscess. From the observations of Marriott, Alden and Lyman, and

Jeans and Floyd, it is now known that an infant may have a severe mastoid infection, capable of producing profound constitutional symptoms, commonly known as "cholera infantum," or even death, without the presence of any of the external signs. After a consideration of the anatomical features of the infant's auditory apparatus, ALDEN (*Arch. Otolaryngol.*, 1927, **5**, 39) again calls attention to a more obscure type of mastoid infection in babies; a type which often eludes detection on account of the absence of external manifestations. The only significant otologic findings, in this group of cases, are a change in the color of the tympanic membrane and a distinct downward sag of the superior canal wall just external to the annulus. The pathologic condition in this type of mastoiditis is not due to pressure, but to a rapid and massive absorption of toxic products. The author believes that, since the majority of the 35 ordinary types of cases coming to operation yielded staphylococci or nonhemolytic streptococci, whereas cultures from the ears of 32 infants with the other, and more obscure, form of mastoiditis almost always showed hemolytic streptococci, a certain bacterial specificity for each form of the disease may exist. He also believes that the failure of the infant's drum to rupture is due to the release of pressure by evacuation of the purulent contents of the middle ear by way of their shorter, straighter and more widely patulous Eustachian tubes and not to the fact that babies' ear drums are thicker. He says that the chief reason for the failure of otologists to recognize this type of mastoiditis in the past has been that these infants are first seen by the pediatrician, who, if he does not appreciate the intimate connection that often exists between obscure aural infection and gastrointestinal disease, fails to call the otologist into consultation. He concludes by stating that "Proper recognition by pediatricians of the significance of this disease combination in the infant and closer study by otologists of infections in the infantile ear will in a few years result in an understanding of the pathology and treatment, and perhaps the prophylaxis of this condition, which will be a material factor in the reduction of infant mortality."

RADIOLOGY

UNDER THE CHARGE OF

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High Colonic Irrigations in the Therapy of Subacute and Chronic Arthritis.—For four years SNYDER and FINEMAN (*Am. J. Roentgenol. and Rad. Ther.*, 1927, **17**, 27) have used colonic irrigations in the treatment

of arthritis with good results, and a combined clinical and roentgenologic study was undertaken to determine the factors responsible for the improvement. It was found that soapsuds enemas would clear out fairly but not completely the residues from a barium meal, while "high" or "low" irrigation was even more effective. In a series of 15 consecutive tests the irrigating tube was passed beyond the sigmoid in 86 per cent. It was proven that the cecum may be reached by the tube. Passage of the tube by experienced hands is not a dangerous procedure, but severe trauma or even puncture of the bowel may occur if the tube is inserted by one who has not had careful and prolonged training. The chief value of inserting the tube into the proximal colon is that it appears in some cases to set up greater contractility of the colon. The paper will be of interest to those who have held that "high" colonic irrigations were impossible.

Intratracheal Injection of Iodized Oil.—The transglottic, subglottic, bronchoscopic and supraglottic methods each have their advantages. PRITCHARD, WHYTE and GORDON (*Radiology*, 1927, **8**, 104) prefer the supraglottic method for adults and have used it in 1000 cases. Injection of iodized oil is indicated: (1) In cases of chronic cough associated with long-standing infection in the upper respiratory tract, particularly sinusitis; (2) cough with purulent expectoration following pneumonia or aspiration of a foreign body; (3) long-standing cough with little expectoration and no frank pulmonary disease; (4) obvious cases of bronchiectasis; (5) bronchial fistulæ; (6) as a therapeutic agent. If the patient swallows any considerable amount of the oil, a glass of hot water containing a dram of soda will act as an emetic. Mild iodism developed in 6 of the 1000 cases. Contraindications for the method comprise acute infections, cold, influenza, active tuberculosis, extensive suppurations if patient is weak, angina pectoris, aneurysm, cardiac decompensation and recent hemoptysis.

Duodenal Ulcer.—A study of the records in the Mayo Clinic over a period of five years by SUTHERLAND (*Radiology*, 1927, **8**, 111) confirms the statement that the stomach more than any other organ is accused of disorders which it never had. During this period approximately 70 per cent of the roentgenologic examinations were negative. Duodenal ulcer is the most common lesion of the alimentary tract seen with the Roentgen ray. The pathognomonic roentgenologic sign of duodenal ulcer is the incisura which deforms the bulbar contour. It may be unilateral or bilateral, and vary from a mere slit to an indentation that nearly bisects the cap. While the deformity has an organic basis, other factors must be concerned in many cases. The other diagnostic sign is the niche. Deformity is seldom observed at the operating table. Roentgenologic deformity persists in patients who have been relieved of all symptoms.

Surgical versus Roentgen Treatment of Exophthalmic Goiter.—CRILE (*Radiology*, 1926, **6**, 365) opened the symposium with a discussion of the surgical treatment. Only three methods, in his opinion, merit serious discussion: rest cure, radiation and surgery. The mortality rate of

thyroidectomy in 1925 in his hands was 0.82 per cent; the resultant scar is invisible within a few weeks. In acute hyperthyroidism time is not a factor, as the patient's occupation should be interferred with and for a sufficient period of time whatever method for diminishing the substance of the gland is employed. The success of any plan of treatment must depend also on the plan of management of the patient over a period of time which varies according to the type of the disease which is under treatment. The preoperative use of iodin has proved to be of considerable value in those cases of hyperthyroidism in which the enlargement of the thyroid is a true hyperplasia. Lahey stressed a point which is of the greatest importance in dealing with goiter, that the basis of all sound thyroid treatment is diagnosis, and that is based upon sound clinical judgment, an attainment only acquired by an extensive experience with thyroid states. It may be so simple to demonstrate that no one could miss it, or may tax the clinical resources of the most experienced observers. Colloid goiter rarely requires surgical treatment; adenomata of the thyroid should be removed in all patients over thirty years of age, because of the danger of malignant degeneration. In adenomata some of the best results in a palliative way from Roentgen ray treatment are seen. Every cystic and every adenomatous goiter should be carefully roentgen-rayed and investigated clinically for intrathoracic or low-lying tumor or cyst of the thyroid. The employment of casual surgery in the hands of an individual not equipped for the special study and operative and postoperative care of these conditions will yield poor results. Hamilton considered the first in importance to be the correct diagnosis of toxic symptoms. Obscure thyroid toxicity can suggest heart disease, diabetes, pulmonary tuberculosis, nausea and vomiting of pregnancy and even acute surgical abdominal conditions. The differentiation of thyroid toxicity from neurasthenic states is a constant problem in a thyroid clinic. It is, however, possible for any physician by long association with thyrotoxic cases to learn to value clinical signs and points in history, so that the majority of doubtful cases can be separated satisfactorily. Basal-metabolism estimations are the only generally accepted indirect laboratory test of thyroid toxicity in present use. Undoubtedly toxic cases as a group have high basal metabolism, and nontoxic patients, including those cured of toxicity, have, as a group, normal readings. But falsely high metabolism tests are very common. The patient must be kept in the hospital at least overnight before the test. One must not accept either a single high or normal basal-metabolism test as evidence of present or absent toxicity, when it does not check with physical signs and history. The test must often be repeated on consecutive days many times before the true basal metabolism can be determined. About 35 per cent of toxic patients have a serious disorder of the heart beat. The auricular fibrillating, as a group, have withstood well the brief strain of surgical treatment and convalescence. Many of the group with auricular fibrillation have congestive heart failure—true decompensation. They have a distinctly short expectation of life, if untreated; properly prepared, they survive surgical treatment. Graham confined the designations (*a*) exophthalmic goiter and (*b*) toxic adenoma to the clinical state of patients but not to the condition of the thyroid gland, and discussed the factors of etiologic

importance. Surgeons and radiologists should have a clear understanding of the pathology of the thyroid and the relation of this organ to toxic goiter. The changes that take place in the thyroid in toxic goiter are in part physiologic and in part pathologic. The former includes hypertrophy, hyperplasia and involution. The latter includes the degenerations, atrophy and fibrosis, inflammations and malignant disease. Any or all of these processes may occur in the thyroid in some cases of toxic goiter. There is a definite use for iodin after operation to prevent regeneration hyperplasia in those glands not completely involuted before operation. The present state of our knowledge concerning the effect upon the thyroid of Roentgen ray and radium irradiation is too unsatisfactory to warrant definite conclusions. In a general way, there is clinical and experimental evidence to indicate that irradiation produces adhesions between the thyroid and surrounding structures; that fibrosis of varying degrees occurs; that vascularity decreases; that the volume of the thyroid diminishes. Jenkinson acknowledged the limits of radiation. That there are cases that respond to surgery is a known and accepted fact; that some patients respond to and get well under rest is also a known fact; that there are cases that can be cured by Roentgen rays is also true. In refractory cases the close coöperation of the surgeon, internist and roengenologist is imperative. It is a well-established fact that in the treatment of exophthalmic type of goiter the Roentgen rays are of great value, and in the majority of cases a cure can be obtained. Many of the cases now operated upon would do better under Roentgen therapy. Burns following Roentgen ray therapy have been a much-advertised argument opposed to this form of treatment. In 500 cases over a ten-year period he had never seen a burn or even a marked erythema, myxedema or parathyroid injury. Improvement is apparent in some cases within ten days after the first series; in the majority of patients within three weeks. Dunham considered Roentgen ray treatment the therapy of choice. Roentgen ray is slow but it is sure. The handling of the case either surgically or radiologically requires unusual technique and a knowledge of psychology of these cases. Many cases of malignancy develop after operation on the thyroid; he had never seen a case of malignancy secondary to Roentgen ray treatment of the thyroid. He treated the thymus; whether benefit is direct or by secondary radiation upon the thyroid he questioned. Patients with exacerbations during menstruation should have the ovaries rayed. Christie stressed the vital importance of correct diagnosis. The results in toxic adenoma are not as brilliant as those in exophthalmic goiter by radiography.

Primary Infection in Tuberculosis.—STOLOFF (*Am. J. Dis. Child.*, 1927, **33**, 363) gives a statistical analysis of over 6000 fluoroscopic examinations of children in the outpatient department of the Children's Clinic at the University of Vienna. In 584, or 9.27 per cent, a single, primary, pulmonary focus was demonstrable, and multiple foci were found in 27. The foci were mostly on the right side and in the lower lobes. Regional disease of the hilum glands was found in 72 per cent of these cases. Pleuritic involvement was observed in only 0.05 per cent. In the beginning the primary focus may not be recognized as

such. In the healed stage it is seen as an area usually the size of a pea and of calcium density, sharply circumscribed, stellate, circular or oval, with an irregular or smooth margin. Normal hilum glands do not cast a shadow. A shadow in the region of the hilum caused by enlargement or disease of the bronchial lymph glands is not necessarily tuberculous. It may be assumed to be tuberculous: (1) When a primary focus of infection is recognized in the region which it drains; (2) when it presents a shadow which is circumscribed with relatively sharp outline, which shows arching and notching, which is of more or less uniformly increased density, and which projects laterally into the lung fields; or (3) when the hilum region presents a hazy appearance of increased density and is spotted, with dense shadows of sharp but irregular contour and varying size. Stripelike shadows lying between the primary focus and the hilum, or pleuritic involvement in the region of the primary focus may be present and aid in the diagnosis. The diagnosis of primary tuberculosis is to be made only when the patient reacts positively to the tuberculin test. All of Stoloff's patients who revealed a primary focus gave positive reactions to tuberculin.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Prevention of Rheumatic Heart Disease.—ALLEN (*J. Roy. San. Inst.*, 1925, **46**, 179) states that of 444,785 deaths in England and Wales in 1923, 56,866, or 12.7 per cent, were due to diseases of the heart. The figures do not give the etiologic factors, but from an enquiry carried out over ten years on patients suffering from heart disease admitted to the wards in the Western Infirmary, it was found that about 60 per cent owed their origin to rheumatic disease. If this figure is applied to the deaths from heart disease, then over 30,000 of these must be the result of the late effects of rheumatism. The incidence of rheumatic infection and rheumatic heart disease in the general population and in childhood can only be very approximately assessed. The per cent of the school population in England and Wales affected with organic heart disease was about 0.8 per cent in 1922, according to the report of the Board of Education. From this it may be estimated that there are about 50,000 children of school age who are suffering from organic heart disease. In addition, 1.3 per cent were suffering

from functional disorders. One must further take into account the number of children who, because of heart disease, are not able to attend school. Thus, in London County Council area, of 2902 absent for over three months, in 23 per cent the cause was rheumatism, rheumatic heart disease or chorea. With the possible exception of cases of congenital heart disease, organic heart disease in childhood may be considered as definitely due to rheumatism. In rheumatism in the child, joint pains are not an essential part of the clinical picture of rheumatism. In fact, many of the symptoms of rheumatic heart disease in the child do not declare themselves in a definite fashion. Indefinite symptoms are undue pallor, some loss of flesh, restlessness and nervousness. A complaint of aching limbs, shortness of breath, pain in the chest or sore throat should be regarded very seriously. The following lines of attacking the problem are suggested: Education of parents, nurses, teachers and doctors as to the significance of the minor or passing ailments which may really be rheumatic in their nature; the inclusion of rheumatism as a disease in the schedule of the Board of Education; prolonged convalescence after an attack of rheumatism; inspection and reinspection; provision of hospital schools for rheumatic cardiac and other cases; provision of open-air day schools for the physically defective.

Oral Hygiene in Relation to Tuberculosis.—CIPES (*Dental Cosmos*, 1926, **68**, 50) states that of 1045 patients examined when admitted to the Bedford Sanatorium for tuberculosis during the last three years (1922–1925) 20 per cent were in the first stage, 40 per cent were in the second stage and 40 per cent were in the third stage of pulmonary tuberculosis. Roentgenograms were taken of all crowned teeth and teeth with nonvital pulps. Of these teeth 70 per cent were found to be possible foci of infection according to the evidence given by the roentgenograms. The percentage of carious teeth and unhealthy gums among these patients is far above that of any group in a like station of life not afflicted with tuberculosis. Poor mouth hygiene, as evidenced by neglected teeth and diseased gums, is a real contributing factor in the etiology of tuberculosis. Patients suffering from pulmonary tuberculosis present a characteristic type of erosion cavity, the severity of which is dependent upon the progress of the tubercular lesion. The question of the disturbance in calcium metabolism and the alteration in the composition of the saliva in tuberculosis is now the subject of investigation by the writer and his associates.

Organization of the Health Program of a University.—SMILEY (*U. S. Pub. Health Rep.*, 1926, **41**, 2631) describes the public health practice and teaching and illustrates by diagrams the relationships to the various local and university agencies. The type of the professional service required is shown by the following quotation: "The development of the health educational program in the university department of health we have found at Cornell to be almost entirely a job for physicians, not nurses—for young physicians, not retired practitioners—for physicians interested in health education and preventive medicine rather than specialists or those interested primarily in therapy. We have found that full-time physicians are preferable to part time, that men physicians

are preferable for men and women physicians for women, that regular professorial ratings in terms of instructorships, assistant professorships, and professorships are preferable to other ratings, and that a schedule permitting each man to distribute his energy over the five fields of physical examination, medical consultation, communicable-disease control, instruction in hygiene and preventive medicine, and research, was preferable to directing his energy to any one field alone." What a college student should know about health is summarized by Dr. Livingston Farrand, President of Cornell, as follows: He should have a knowledge of the physiological basis for sound health habits, such as regular and sufficient hours of sleep, right posture, suitable exercise, and proper elimination. He should know the types, amounts, and proportions of the various food elements essential to the proper nurture of his body. He should have an acquaintance with the principles of normal mental action and the conditions underlying the more common variations from normal state of mind. He should have a general understanding of the sex instinct—its stages of development, its normal expression, and the values and penalties attaching to it. He should have a knowledge of the factors determining infection and resistance and the principles of artificial immunization in the case of certain of the common infectious diseases. He should have enough knowledge of the causes and prevention of the degenerative diseases to offer a prospect of passing through middle life without a breakdown. He should know, and therefore be armed against, health hazards lurking in the environment, such as polluted water and milk supply, congestion in housing, poisonous dusts of certain industries, infected soil, etc. He should appreciate the necessity for frequent medical and dental examination. He should have an intelligent basis for choosing wisely his medical and dental advisers, and for realizing that the modern practice of medicine is grounded on science and not on mystery, fancy, and tradition. He should have a knowledge of the important health problems facing the community, of the methods of attacking those problems, and of the results to be expected from intelligent community action in the public health field.

Pneumonia in Pittsburgh.—TOMANEK and WILSON (*Proc. Am. Phil. Soc.*, 1924, **63**, 279) state that the death rate from pneumonia (all forms) in the ten original registration states of 1900 has remained stationary or declined slightly during the period 1900 to 1920; in Pittsburgh the rate, starting at about the general level, has climbed at a fairly steady rate to around 350, about doubling in twenty years. The calculated trend for Pittsburgh was +10 per 100,000 *per annum* while that for the ten states was −0.4. Distribution of the population of Pittsburgh by age in 1900, 1910 and 1920 shows that the population is growing older. The death rates by age groups for bronchopneumonia and pneumonia all forms are increasing at all ages, however, while lobar and undefined pneumonia is increasing in all groups other than infancy and the group naught to four years. The rate of increase of the pneumonia mortality is greatest in just those ages, twenty to fifty years, which are economically the most important with respect to labor and the rate of increase averages over 5.5 per cent *per annum* for the whole period, twenty to sixty years. The unhygienic

housing in Pittsburgh, the severe labor conditions in the city, the importation of labor into the city, the excess of smoke and dust due to the great industrial activity, and the possibility of a tendency to report pneumonia as a cause of death relatively more frequently than is customary are discussed as accountable for the high and increasing pneumonia rate. It is believed that all of these factors probably contribute to Pittsburgh's excess mortality from this disease, but it is difficult to admit that they are progressively becoming unfavorable enough to afford a rational explanation for any considerable part of the increase. It seems highly probable that smoke and dust may act accumulatively, so as to produce not only an excess death rate but an increase in it, continuing possibly even after there has been some improvement in the control of the smoke and dust nuisance. It seems also highly probable that there is a tendency to report pneumonia as a cause of death somewhat more freely than elsewhere. No satisfactorily sure conclusions can, however, be reached as to the cause of Pittsburgh's excess mortality from pneumonia or its increase without a prolonged carefully controlled scientific study of all phases of the situation, social, statistical and in particular physical and physiologic.

The Chlorin Treatment of Contaminated Oysters.—KRUMWEIDE, PARK, *et al.* (*Am. J. Pub. Health*, 1926, **16**, 142) state that the chlorination treatment of contaminated oysters will result in a marked diminution in the number of B. typhosus, but even six successive treatments may not rid the oysters of the contaminating pathogens. The process cannot be recommended, therefore, in any sense as a reliable means of "sterilizing" contaminated oysters and thus rendering them safe for consumption. The results indicate that safe oysters can only be produced by growing them in waters uncontaminated by human feces.

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